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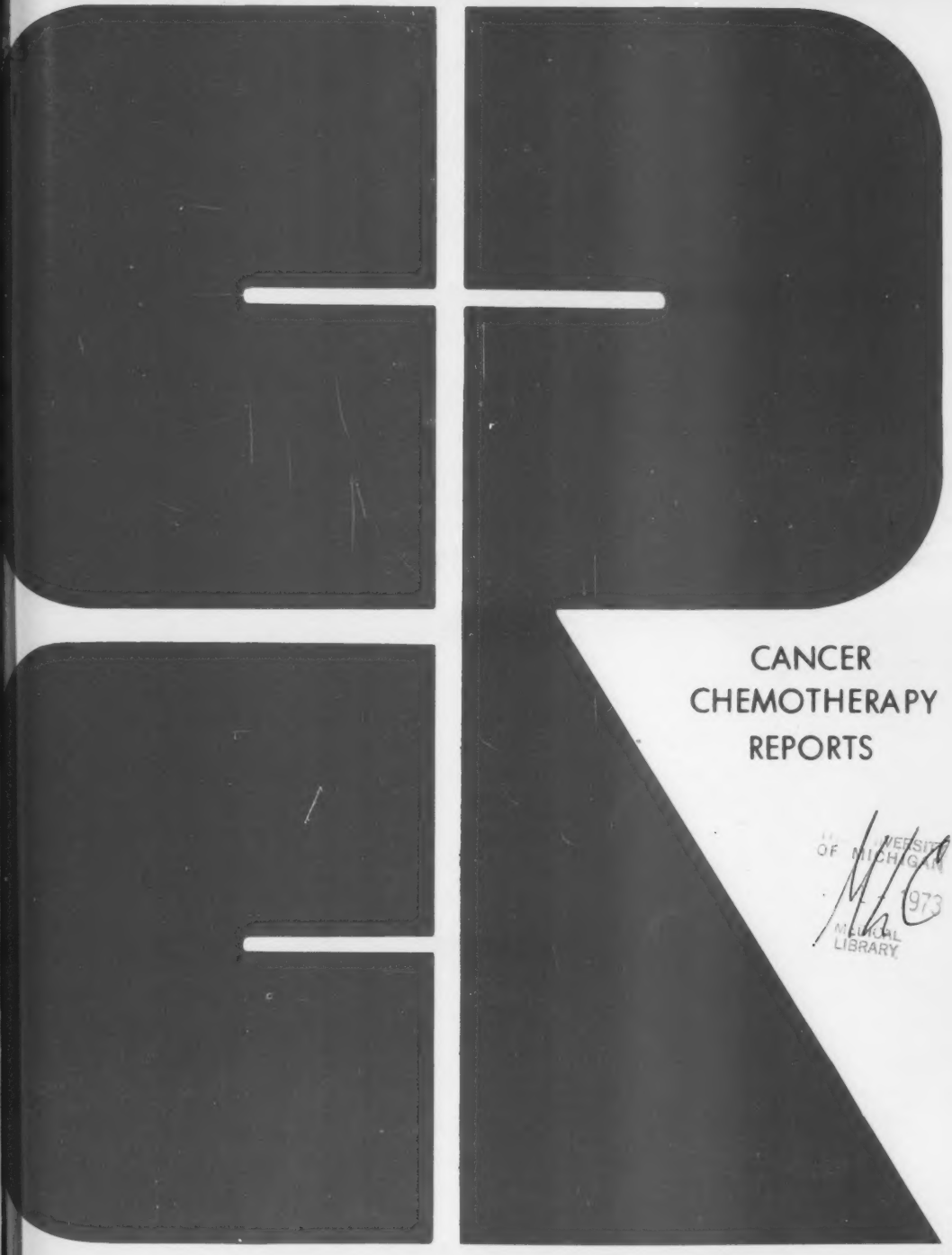

CANCER CHEMOTHERAPY REPORTS

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Hazleton Laboratories, Vienna, Virginia, April 14, 1972

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The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through November 30, 1973.

Evaluation of Antileukemic Agents in Advanced Leukemia L1210 in Mice. X [1,2]

Ira Kline,[3] Miriam Gang,[3] Denis D. Tyrer,[3] John M. Venditti,[4] E. Waynn Artis,[3] and Abraham Goldin [4,5]

Sixty-seven compounds were tested for their ability to prolong survival time in mice with advanced systemic leukemia L1210. Acetamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis- (NSC-18269) and imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]- (NSC-82196), evaluated for the first time in this assay system, were 74% and 176% as effective as methotrexate (NSC-740) which was used as a standard for antileukemic activity. The previously reported marked activity of urea, 1,3-bis(2-chloroethyl)-1-nitroso- (BCNU; NSC-409962) and urea, 1-(2-chloroethyl)-1-nitroso- (NSC-47547) in this assay system was confirmed in these studies. Moreover, eight additional nitrosourea derivatives were tested and exhibited marked antileukemic activity. Data are also presented on the influence of time of treatment initiation, schedule of treatment, and route of drug administration on the therapeutic effectiveness of antitumor compounds of interest, including imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)- (NSC-45388), cytosine arabinoside (NSC-63878), 6-methylmercaptopurine riboside (NSC–40774), and six nitrosourea derivatives.

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[3] Microbiological Associates, Inc., Bethesda, Md.

[4] DR&D, DCT, NCI, Bethesda, Md.

[5] The authors are grateful to Dr. Vaman S. Waravdekar, Nathan Mantel, James Morse, Gary Hoffman, Coralia Flaifel, and Ann Smith for their suggestions and help in preparing this manuscript. The following also provided valuable assistance in carrying out the experiments: Eugene Allen, Brenda Boldin, Barrington Butts, Eugene Dantley, David Elam, Charles Ester, Sidney Green, Milford Greene, Herman Hairston, Emma Harrison, Claudest Jones, Nathan Kight, Otha Taylor, Wilma Todd, Nathaniel Tolson, and Carl VonDerPool.

This report is the tenth in a series (1–9) presenting data obtained using a survival time assay for the quantitative evaluation of the relative effectiveness of chemical agents against systemic leukemia L1210. Similar assay systems were used to evaluate drug effectiveness against resistant variants of leukemia L1210 (10). The assay (11–14) permits the evaluation of the antileukemic activity of the compounds in relation to methotrexate (NSC-740), which is used as a standard for therapeutic activity. In the 32 experiments included in the present study, 58 compounds not previously evaluated in this system are rated according to their effectiveness in increasing the median survival time (MST) of mice with advanced leukemia L1210 on a schedule of daily subcutaneous (sc) administration. Ten compounds previously reported (1,2,5–9) were studied further. Also included are data on the influence of the time of treatment initiation, schedule of treatment, and route of drug administration.

MATERIALS AND METHODS

The materials and methods are essentially the same as described in previous reports from this laboratory (1–9). In most experiments, a saline suspension of cells prepared from leukemia L1210-infiltrated spleens of DBA/2 stock tumor mice was implanted (0.1–0.2 ml/mouse) sc into the right hind leg of BDF_1[6] or CD_2F_1[7] hybrid male mice; in a few specifically noted instances recipients were DBA/2 mice. The strain, sex, and weight range of the mice and the level of leukemic inoculum used in each experiment are shown in the tables. Each experiment involved treated and untreated mice that received the experimental tumor inoculum and untreated mice that received serial dilutions of the inoculum. Data from the latter groups showed that

[6] BDF_1 = (C57BL/6 female × DBA/2 male)F_1.

[7] CD_2F_1 = (BALB/cAn female × DBA/2 male)F_1.

in each of the experiments the experimental tumor inoculum was at least ten times that required to kill 100% of untreated mice.

Treatment (except where specifically noted in the tables) was begun when the local tumor at the site of sc leukemic inoculation was estimated by manual palpation to be 7 mm in diameter. This occurred 2–5 days prior to the median day of death of the untreated controls. On the day treatment was initiated in each experiment, three to six mice taken randomly from the population that had received the experimental leukemic inoculum were killed and their spleens implanted sc into normal mice of the same strain. Consistent death from tumor of the implant recipients indicated that the disease was systemic in the donor mice. The MSTs for the recipients of the splenic tissue are reported in the tables relative to the day of splenic inoculation.

Each compound tested, its molecular formula, the vehicle in which it was given, and the dose (mg/kg/injection) are given in the tables of results (table 12).

Generally, the compounds were injected sc in the scapular region at a constant volume of 0.01 ml/g of body weight and given until death. Instances in which an alternative schedule or route of treatment was used are noted in the tables.

The drugs were administered over a wide range of logarithmically spaced dose levels. Typically, as the dose level was increased for an active compound, there was an increase in the MST of the leukemic mice. With further increase in dosage, the toxicity of the drug for the host became limiting and resulted in a diminution in MST. The relative effectiveness of the various therapies was based on the increase in MST at the optimal dose of each drug (ie, the dose providing the maximum increase in MST). Where the maximum MST was observed at more than one dosage level, selection of the optimal dose was based on the entire individual survival pattern. Instances in which the optimal dose may be outside the range of doses employed are noted in the tables by the symbol * or †. Where all dose levels were toxic as evidenced by body weight loss (denoted by the symbol *), the optimal dose may be lower than any used. Where no clear evidence of toxicity appeared at any dose level tested (indicated by the symbol †), the optimal dose may be higher than any employed. In some cases, although the maximum MST occurred at one of the extreme dosage levels, the data indicated no advantage in testing at still more extreme levels. Such instances are not noted specifically.

The efficacy of methotrexate in increasing survival time of leukemic mice was used as a standard for rating compounds as to antileukemic effectiveness. The relative efficacy of each test compound was computed in percent as $(M_t-M_c)/(M_s-M_c) \times 100$, where M_t is the MST at the optimal daily dose of the test compound, M_s is the MST at the optimal daily dose of the methotrexate standard, and M_c is the MST of untreated controls.

Two ratings are shown in studies on the influence of the route of drug administration or the schedule of treatment on antileukemic effectiveness; ie, the compounds are rated relative to (*a*) the daily sc administration of the methotrexate standard and (*b*) the MST of untreated controls. The MST of untreated controls is calculated as $(M_t-M_c)/(M_c) \times 100$.

RESULTS

A. Relative Effectiveness of Compounds Given Sc Daily Against Advanced Leukemia L1210

1. Alkylating agents (table 1, section 1; table 12, expts DL–500, 514, 526, 536, 541, 545, 550, 555, 556, 564, 584, 590, 596, 607): Fourteen alkylating agents were studied for the first time in this advanced L1210 assay system. Two agents, acetamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis- (NSC-18269) and 2,3-butanediol, 1,4-bis[(2-chloroethyl)amino]-, dihydrochloride, DL- (NSC-83290) were 74% and 58% as effective respectively as methotrexate. The remaining agents were less than 50% as effective as methotrexate. Nonane (NSC-3052) activity shown here agrees with previous results (1,5,6).

2. Imidazole carboxamide derivatives (table 1, section 2; table 12, expts DL–521, 530, 536, 556): Imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]- (NSC–82196), one of a new class of antitumor agents, exhibited marked activity against early mouse leukemia L1210 and displayed inhibitory activity against Sarcoma 180, Adenocarcinoma 755, and Walker

256 carcinosarcoma (15). In the advanced leukemia L1210 assay system reported here, daily sc treatment with this agent resulted in a 3.5-fold increase in lifespan over the untreated controls and a 1.5-fold increase over the survival time obtained with methotrexate. The influence of the route of administration and schedule of treatment on the antileukemic activity of this agent is discussed fully elsewhere (16).

A methylester analog (NSC-87982) and a dimethyl analog (NSC-45388) of NSC-82196 were less effective against advanced leukemia L1210 (expts DL-521, 530, 536; tables 1 and 12). The data for NSC-87982 indicate, however, that doses higher than any employed in this study may result in greater antileukemic activity. When treatment with NSC-45388 was started early (on Day 3), the maximum MST of the mice was 3 days greater than that observed when treatment was started late (on Day 7). Furthermore, a smaller amount of drug given daily was required to give the best response (expt DL–530, table 12).

3. Nitrosourea derivatives (table 1, section 3; table 12, expts DL–496, 499, 500, 514, 550, 556, 564, 568, 584, 585, 607): The marked antileukemic activity reported previously for BCNU (NSC-409962) and urea, 1-(2-chloroethyl)-1-nitroso- (NSC-47547) (8,9) was also generally observed for the additional related derivatives in this study. Only one of eight new derivatives tested, urea, 3-(*p*-acetylphenyl)-1-(2-chloroethyl)-1-nitroso-(NSC-89207), failed to exceed the antileukemic activity of methotrexate; in one experiment this agent was 60% as effective as methotrexate. It is of interest that the two nitrosoureas with fluoroethyl groups exhibited the same high degree of activity as the nitrosourea with chloroethyl groups. The influence of treatment schedule and route of drug administration on the activity of several chloroethyl nitrosoureas are described in section B.

4. Other urea derivatives (table 1, section 4; table 12, expts DL-496, 500, 514, 556): Compared to methotrexate, urea, 1-hydroxy-1-methyl- (NSC-529064) was approximately 40% as active and urea, 1-ethyl-1-hydroxy- (NSC-50840) was 20% as active. Pseudourea, 2,2′-(9,10-anthrylenedimethylene)bis-[2-thio-, dihydrochloride, dihydrate (NSC-56054) and urea, [α-(2-methylhydrazino)-*p*-toluoyl]-, monohydrobromide (NSC-77517) were ineffective in this system; however, it is possible that the maximally effective doses were not employed.

5. Pyrimidine derivatives (table 1, section 5; table 12, expts DL-481, 483, 484, 505, 523, 544, 584): The antitumor activity of cytosine arabinoside (NSC-63878), a synthetic agent structurally related to the naturally occurring nucleoside of cytosine, has been studied extensively in this laboratory. The marked antileukemic activity of this agent on daily sc treatment against advanced leukemia L1210 has been reported in previous publications in this series (8,9) and is confirmed by the studies in this report. Other reports have presented data on (*a*) the influence of treatment schedule (9, 17,18) and route of administration (19); (*b*) sequential treatment with BCNU (NSC-409962) (20) and cyclophosphamide (NSC-26271) (21); (*c*) effectiveness against the leukemia L1210 variant resistant to methotrexate (22) and against the L1210 variant resistant to imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]- (NSC-82196) (23); and (*d*) effectiveness against intracerebrally (ic) implanted cells (24).

The effect of the schedule of treatment and route of administration on the antileukemic activity of cytosine arabinoside (NSC-63878) and the effectiveness of the triacetate derivative, ara-C triacetate (NSC-93150), given orally, are discussed in section C.

Compared to methotrexate, orotic acid, 5-fluoro-, monohydrate (NSC-31712) and this agent with the methyl ester group added, orotic acid, 5-fluoro-, methyl ester (NSC-64333), were 40% and 33% as effective against leukemia L1210 respectively. Pyrimidine, 2,4,5-triamino- (NSC-65987), which previously displayed no antileukemic activity (9), was retested at higher doses and found again to be ineffective. 2,5-Pyridinedicarboxanilide, 4′,4″-bis(1,4,5,6-tetrahydro-2-pyrimidinyl)-, dihydrochloride, dihydrate (NSC-80362) displayed no activity at any of the doses tested, but the data do not indicate that this agent should be retested at still more extreme levels.

6. Purine derivatives (table 1, section 6; tables 2, 3, and 12, expts DL–496, 498, 502, 510, 514, 521, 533, 536, 541, 545, 555, 564, 618): Compared to methotrexate, 9*H*-purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2′,3′,5′-tributyrate (NSC-76955), an analog of thioguanosine

(NSC-29422), was 50% as active against leukemia L1210, which is comparable to the activity previously reported for thioguanosine (2,4) and 6-MP (NSC-755). Two additional analogs of thioguanosine, 9*H*-purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-tris(*p*-chlorobenzoate) (NSC-76954) and 9*H*-purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-trispropionate (NSC-77556), were less effective, but in both instances it is possible that higher doses may be more effective. Similarly, with the purine-6-thiol, disodium salt, compd. with bismuth oxide (BiO) (3:1), trihydrate (NSC–70088), an analog of 6-MP (NSC-755), higher doses may elicit a rating greater than the 28% reported here.

Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α'-(hydroxymethyl)-, monohydrochloride (NSC-49928) and guanazole (NSC-1895), not previously evaluated in this assay system, were about 30% as active as methotrexate. It should be noted that the best effect with guanazole was obtained with the high daily dose of 2000 mg/kg. In other experiments in this laboratory with the early L1210 system (ascites cells implanted intraperitoneally [ip]; treatment ip from Day 1), guanazole was more effective when administered every 12 hours than when given once daily.

The activity of 6-methylmercaptopurine riboside (NSC-40774) against advanced L1210 on daily sc treatment reported here (approximately 30% as active as methotrexate), is in agreement with earlier reports (7). The influence of the route of administration and schedule of treatment on the activity of this agent in normal and leukemic mice is summarized in table 2 and shown in detail in table 12, expts DL–498 and DL–502.

6-Methylmercaptopurine riboside (NSC-40774) was about equally effective on sc and oral administration (table 2, expt DL–498). Although this agent was ineffective when given ip and intravenously (iv), higher doses may result in greater activity. In this advanced assay system, 6-methylmercaptopurine riboside was more effective when given daily than when given twice daily, every second or every fourth day, or as a single treatment (table 2, expt DL–502). Therapeutic dose levels with each treatment schedule and route used produced lethal toxicity in normal mice.

Data from an experiment with our early L1210 system (ascites implanted ip; treated ip Days 1–17) indicated that widely spaced injections with 6-methylmercaptopurine riboside may be therapeutically advantageous. In expt DL-618, summarized in table 3 and shown in detail in table 12, oral or ip treatment of mice inoculated with splenic L1210 was started early (Day 3). With oral administration, the best effect was obtained when the agent was given every 7 days (110% increase in MST over controls as compared with 50%, 60%, or 75% with daily treatment, treatment every 3 days, or one treatment only). With ip administration, approximately equal results were obtained with treatment every 3 or 7 days or with one treatment only (60%, 70%, and 65% increase in MST over controls). Daily ip treatment, however, resulted in a substantially reduced response.

Guanosine, 2'-deoxy- (NSC-22837) and purine, 2-amino-6-[[6-chloro-2-(ethylthio)-4-pyrimidinyl]thio]- (NSC-52385) displayed no activity at the highest doses tested. There is, however, evidence in both instances that the maximum effective doses were not employed.

7. Antibiotics (table 1, section 7; table 12, expts DL-484, 502, 505, 514, 550): Actinobolin (NSC-31083), at a high daily dose of 833 or 1388 mg/kg, was previously reported in this assay system to be nearly 40% as effective as methotrexate (8,9). In the current experiments, the activity of actinobolin with more frequent administration was studied. No advantage was observed when it was administered twice daily at 12-hour intervals as compared with once daily (expt DL-484).

The remaining two antibiotics in this study, neocarzinostatin (NSC-69856) and streptozotocin (mixture) (NSC-37917), were essentially ineffective against the advanced L1210 tumor.

8. Other compounds (table 1, section 8; table 12, expts DL-484, 496, 499, 500, 514, 520, 521, 524, 526, 530, 533, 536, 541, 556, 590, 596): Treatment with *p*-cymene-2-sulfonic acid, 5-hydroxy-, compd. with 1,1'-[(methylethanediylidene)dinitrilo]diguanidine (2:1) (NSC-69185) prolonged the MST of the mice 4 days beyond that of the untreated leukemic controls for an increase of 32% relative to methotrexate. A 28% increase in MST relative to methotrexate was obtained with acridine, 9-[*p*-(dimethyl-

amino)anilino]- (NSC-13002), but the data indicate that higher doses may elicit a greater effect. The remaining compounds were relatively ineffective.

B. Influence of Schedule of Treatment and Route of Administration on Nitrosourea Derivatives

(Tables 4, 5, 6, and 12, expts DL-499, 568, 585): The previously reported effectiveness of BCNU (NSC-409962) over a wide range of treatment schedules (8) was confirmed in the current experiments (tables 4, 5, and 12, expts DL-499, 585). In agreement with our previous findings (9), urea, 1-(2-chloroethyl)-1-nitroso- (NSC-47547) on daily sc treatment displayed marked antileukemic activity comparable to that observed for BCNU (NSC-409962) (table 4, expt DL-499). In contrast to BCNU (NSC-409962), however, a marked diminution in activity was observed when NSC-47547 was administered weekly or one time only. In the same experiment (tables 5 and 12, expt DL-585), urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (CCNU; NSC-79037) and BCNU (NSC-409962) displayed equal effectiveness when given daily, weekly, or one time only.

With BCNU (NSC-409962) and NSC-47547, the maximum effect via any of the treatment schedules studied was obtained with dose levels lethal to the normal mice. With CCNU (NSC-79037) administered daily, the optimal daily dose was fatal to the normal mice; when administered weekly or one time only, the optimal dose produced no fatalities among normal mice.

Our previous report (9) showed that the marked effectiveness of a single sc treatment with BCNU (NSC-409962) was retained when this agent was administered orally or ip. In the current experiment (tables 6 and 12, expt DL-568), the maximum antileukemic activity of this drug and four additional nitrosoureas (NSC-79037, NSC-88106, NSC-87974, and NSC-88104) on daily sc administration was retained on daily oral treatment. The optimal daily oral dose for NSC-88104 was slightly greater than the optimal daily sc dose. For the other nitrosoureas in this group, the optimal daily dose was the same by either route.

C. Influence of Schedule of Treatment and Route of Administration on Cytosine Arabinoside (Ara-C; NSC-63878)

(Tables 7-10, expts DL-481, 483, 523, 544): Previous reports in this series have shown that cytosine arabinoside (NSC-63878) is more effective against advanced L1210 leukemia when administered sc four times daily, two times daily, or every 2 or 4 days than when given weekly or one time only (8,9,17). Our data (expt DL-483, tables 7 and 12), which show the marked reduction in antileukemic effectiveness when cytosine arabinoside (NSC-63878) is given as a single treatment as compared with multiple schedules of treatment, are discussed more fully elsewhere (17).

The influence of the route of administration of the effectiveness of cytosine arabinoside (NSC-63878) is discussed in detail in another report (19). In expt DL-481 (tables 8 and 12), daily treatment with the agent for advanced leukemia L1210 was less effective administered orally than sc, ip, or iv. The effect of more frequent oral and sc administration of the drug was studied in expt DL-523 (tables 9 and 12). Sc treatment with this agent four or two times daily was more effective than one daily treatment. On the other hand, oral treatment was nearly equally effective whether given one, two, or four times daily and was, in each instance, markedly less effective than sc treatment. In expts DL-481 and DL-523 (tables 8 and 9) the oral optimal doses were greater than the sc doses. In contrast to sc administration, the maximum effects with oral administration were generally obtained with dose levels toxic to normal mice.

The effect of acetate groups on the antileukemic activity of cytosine arabinoside (NSC-63878) administered orally was studied in expt DL-544 (tables 10 and 12). Ara-C triacetate (NSC-93150) given sc was 69% as effective as the parent compound administered sc, but its activity was not significantly diminished when given orally. Orally, the two agents displayed similar effectiveness, although a higher dose of ara-C triacetate (NSC-93150) was required.

Skipper et al (25) reported that in mice inoculated ip with 10^5 ascites cells, ip treatment with cytosine arabinoside (NSC-63878) every 3 hours every 4 days was more effective than ip treatment with a single dose either

every 4 days or daily. We used the same L1210 ascites system to compare the oral activity of a single dose of cytosine arabinoside (NSC-63878) and ara-C triacetate (NSC-93150) administered on Day 1 only, daily, or every 4 days (1-9) with divided doses (injection every 3 hours for 24 hours) on Day 1 only or every 4 days (table 11).

The maximum increase in survival time with cytosine arabinoside (NSC-63878) administered orally was obtained when the agent was given every 3 hours for 24 hours on Days 1, 5, and 9. The MST was only slightly greater than that obtained with a single dose every 4 days, but appreciably greater than the MST obtained with the other treatment schedules used.

Ara-C triacetate (NSC-93150), on the other hand, was most effective when given as a single dose every 4 days. This treatment, however, was not greatly superior to treatment in divided doses every 4 days or to single-dose daily treatment. Of particular interest is the observation that with both agents treatment in divided doses required a much smaller amount of drug daily to achieve the maximum response than did single-dose treatment.

TABLE A.—List of compounds tested*

Entry No.	NSC No.	CAS reg. No.	Compound	Molecular formula	Source†	Table No.
89909	740	—	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-(methotrexate)	$N_8O_5C_{20}H_{22}$	229A	1–12
89910	1895	503–88–8	1,2,4-Triazolidine, 3,5-diimino-(guanazole)	$N_5C_2H_5$	51D	1, 12
89911	3052	4248–77–5	1,9-Nonanediol, dimethanesulfonate (nonane)	$O_6S_2C_{11}H_{24}$	49P	1, 12
89912	13002	13365–38–3	Acridine, 9-[*p*-(dimethylamino)-anilino]-	$N_3C_{21}H_{19}$	2	1, 12
89913	18269	7575–18–0	Acetamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]-bis-	$N_4O_4C_{14}H_{18}$	233B	1, 12
89914	18270	4014–60–2	*p*-Benzoquinone, 2,5-bis(1-aziridinyl)-3,6-diethoxy-	$N_2O_4C_{14}H_{18}$	233B	1, 12
89915	18274	—	Butyramide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]-bis-	$N_4O_4C_{18}H_{26}$	233B	1, 12
89916	22837	—	Guanosine, 2'-deoxy-	$N_5O_4C_{10}H_{13}$	7P	1, 12
89917	31083	24397–89–5	Isocoumarin, 4-(2-aminopropionamido)-3,4,4*a*,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-(actinobolin)	$N_2O_6C_{13}H_{20}$	27C	1, 12
89918	31712	—	Orotic acid, 5-fluoro-, monohydrate	$N_2O_4FC_5H_3 \cdot HOH$	217P	1, 12
89919	37917	—	Streptozotocin	$N_3O_{12}C_{14}H_{27}$	35	1, 12
89920	40774	7143–67–1	9*H*-Purine, 6-(methylthio)-9-β-D-ribofuranosyl-, dihydrate (6-methylmercaptopurine riboside)	$N_4O_4SC_{11}H_{14} \cdot 2\ HOH$	4P	1–3, 12
89921	42076	—	Podophyllotoxin, 4,6-*O*-benzylidene-β-D-glucoside	$O_{12}C_{28}H_{32}$	126C	1, 12
89922	42330	—	Glucopyranose, 6-[(2-chloroethyl)-methylamino]-6-deoxy-,hydrochloride, D-	$NO_5ClC_9H_{19} \cdot HCl$	32	1, 12

TABLE A.—List of compounds tested—Continued

Entry No.	NSC No.	CAS reg. No.	Compound	Molecular formula	Source†	Table No.
89923	42343	—	Propionic acid, 3-[*o*-[bis(2-chloroethyl)amino]phenoxy]-	$NO_3Cl_2C_{13}H_{17}$	32	1, 12
89924	44426	—	Acetic acid, [*p*-[bis(2-chloroethyl)amino]phenoxy]-, ethyl ester	$NO_3Cl_2C_{14}H_{19}$	32	1, 12
89925	45388	4342-03-4	Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-	$N_6OC_6H_{10}$	20	1, 12
89926	47547	2365-30-2	Urea, 1-(2-chloroethyl)-1-nitroso-	$N_3O_2ClC_3H_6$	32	1, 4, 12
89927	49271	13156-19-9	2(1*H*)-Pyridone, 1,5-dihydroxy-6-methyl-	$NO_3C_6H_7$	52	1,12
89928	49928	—	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α'-(hydroxymethyl)-, monohydrochloride	$N_5O_4C_{10}H_{11} \cdot HCl$	431B	1, 12
89929	50164	—	Colchicine, demethyl-	$NO_6C_{21}H_{23}$	29A	1, 12
89930	50840	7433-42-3	Urea, 1-ethyl-1-hydroxy-	$N_2O_2C_3H_8$	52	1, 12
89931	51915	—	Cyclohexanecarboxamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis-	$N_4O_4C_{24}H_{32}$	233D	1, 12
89932	52385	—	Purine, 2-amino-6-[[6-chloro-2-(ethylthio)-4-pyrimidinyl]thio]-	$N_7S_2ClC_{11}H_{10}$	261A	1, 12
89933	56054	3063-89-6	Pseudourea, 2,2'-(9,10-anthrylenedimethylene)bis-[2-thio-, dihydrochloride, dihydrate	$N_4S_2C_{18}H_{18} \cdot 2\ HCl \cdot 2\ HOH$	9	1, 12
89934	58404	820-75-7	Glycine, *N*-(diazoacetyl)-, hydrazide	$N_4O_2C_4H_7$	29A	1, 12
89935	60542	110-71-4	Ethane, 1,2-dimethoxy-	$O_2C_4H_{10}$	11P	1, 12
89936	63878	69-74-9	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside)	$N_3O_5C_9H_{13} \cdot HCl$	35D	1, 7-12
89937	64333	1996-54-9	Orotic acid, 5-fluoro-, methyl ester	$N_2O_4FC_6H_5$	261A	1, 12
89938	65005	—	Adenine, 9-[2-[bis(2-chloroethyl)amino]ethyl]-, dihydrochloride, monohydrate	$N_5Cl_2C_{11}H_{16} \cdot 2\ HCl \cdot HOH$	62A	1, 12
89939	65987	3546-50-7	Pyrimidine, 2,4,5-triamino-	$N_3C_4H_7$	62A	1, 12
89940	66796	—	Cyclopentanecarboxylic acid, 1-(2-aminoacetamido)-, monohydrochloride	$N_2O_3C_8H_{14} \cdot HCl$	213B	1, 12
89941	68303	—	1,5-Pentanediamine, *N,N'*-bis(2-chloroethyl)-, dihydrochloride	$N_2Cl_2C_9H_{20} \cdot 2\ HCl$	32B	1, 12
89942	69185	—	*p*-Cymene-2-sulfonic acid, 5-hydroxy-, compd. with 1,1'-[(methylethanediylidene)dinitrilo]diguanidine (2:1)	$O_4SC_{10}H_{14} \cdot \frac{1}{2}\ N_8C_8H_{12}$	57A	1, 12
89943	69856	—	Neocarzinostatin, crystalline antibiotic	Unknown	6C	1, 12

TABLE A.—List of compounds tested—Continued

Entry No.	NSC No.	CAS reg. No.	Compound	Molecular formula	Source†	Table No.
89944	70088	—	Purine-6-thiol, disodium salt, compd. with bismuth oxide (Bi O) (3:1), trihydrate	$N_4SC_5H_4$ • Na salt • ½(BiO) • 3 HOH	209A	1, 12
89945	70631	—	Glutamic acid, *N*-[bis(2-chloroethyl)carbamoyl]-, diethyl ester, L-	$N_2O_5Cl_2C_{14}H_{24}$	613A	1, 12
89946	70806	—	1,3-Propanediamine, *N,N'*-bis-(2-chloroethyl)-, dihydrochloride	$N_2Cl_2C_7H_{16}$ • 2 HCl	32B	1, 12
89947	74944	387-97-3	8-Quinolinol, 5-fluoro-	$NOFC_9H_6$	265A	1, 12
89948	76954	—	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-tris(*p*-chlorobenzoate)	$N_5O_7SCl_3C_{31}H_{22}$	261A	1, 12
89949	76955	—	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-tributyrate	$N_5O_7SC_{22}H_{31}$	261A	1, 12
89950	77517	—	Urea, [α-(2-methylhydrazino)-*p*-toluoyl]-, monohydrobromide	$N_4O_2C_{10}H_{14}$ • HBr	217A	1, 12
89951	77556	—	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-tripropionate	$N_5O_7SC_{22}H_{31}$	261A	1, 12
89952	79037	13010-47-4	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (CCNU)	$N_3O_2ClC_9H_{16}$	20	1, 5, 6, 12
89953	80087	443-30-1	*p*-Toluidine, α-inden-1-ylidene-*N,N*-dimethyl-	$NC_{18}H_{17}$	285A	1, 12
89954	80362	—	2,5-Pyridinedicarboxanilide, 4',4''-bis(1,4,5,6-tetrahydro-2-pyrimidinyl)-, dihydrochloride, dihydrate	$N_7O_2C_{27}H_{27}$ • 2 HCl • 2 HOH	254A	1, 12
89955	81159	—	2,3-Butanediol, 1,4-bis[(*meso*-2-chloro-1-methylethyl)[or (*meso*-2-chloropropyl)]amino]-, dihydrochloride (isomer B), *meso*-	$N_2O_2Cl_2C_{10}H_{22}$ • 2 HCl	32B	1, 12
89956	82196	5034-77-5	Imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]-	$N_6OCl_2C_9H_{12}$	20	1, 12
89957	83083	—	*meso*-2,3-Butanediol, 1,4-bis[(*dl*-2-chloro-1-methylethyl)[or(*dl*-2-chloropropyl)]amino]-, dihydrochloride	$N_2O_2Cl_2C_{10}H_{22}$ • 2 HCl	32B	1, 12
89958	83290	28069-01-4	2,3-Butanediol, 1,4-bis[(2-chloroethyl)amino]-, dihydrochloride, DL-	$N_2O_2Cl_2C_8H_{18}$ • 2 HCl	32B	1, 12
89959	83693	34153-49-6	Butyric acid, 4-[*p*-(3,3-dimethyl-1-triazeno)phenyl]-, hydrazide	$N_5OC_{12}H_{19}$	20	1, 12
89960	86056	14039-10-2	Urea, 3-(1-adamantyl)-1-(2-chloroethyl)-1-nitroso-	$N_3O_2ClC_{13}H_{20}$	20	1, 12
89961	87206	4238-66-8	6*H*-Pyrido[4,3-*b*]carbazole, 5-methyl-	$N_2C_{18}H_{12}$	32B	1, 12

TABLE A.—List of compounds tested—Continued

Entry No.	NSC No.	CAS reg. No.	Compound	Molecular formula	Source†	Table No.
89962	87974	13908–93–5	Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso-	$N_3O_2FC_9H_{16}$	20	1, 6, 12
89963	87982	10197–64–5	Imidazole-4-carboxylic acid, 5-(3,3-dimethyl-1-triazeno)-, methyl ester	$N_5O_2C_7H_{11}$	20	1, 12
89964	88104	13909–12–1	Urea, 3-2-chlorocyclohexyl)1-(2-chloroethyl)-1-nitroso-, *trans*-	$N_3O_2Cl_2C_9H_{15}$	20	1, 6, 12
89965	88106	13909–13–2	Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso-	$N_3O_2ClC_{10}H_{16}$	20	1, 6, 12
89966	89207	13909–27–8	Urea, 3-(*p*-acetylphenyl)-1-(2-chloroethyl)-1-nitroso-	$N_3O_3ClC_{11}H_{12}$	20	1, 12
89967	90439	16063–79–9	Valine, 4,4,4-trifluoro-, DL-	$NO_2F_3C_5H_8$	304B	1, 12
89968	90440	2792–72–5	Leucine, 5,5,5-trifluoro-, DL-	$NO_2F_3C_6H_{10}$	304B	1, 12
89969	91741	329–71–5	Urea, 1-(2-chloroethyl)-1-nitroso-3-(2,6-xylyl)-	$N_3O_2ClC_{11}H_{14}$	20	1, 12
89970	93150	—	Cytosine, 1-β-D-arabinofuranosyl-, 2′,3′,5′-triacetate (ara-C triacetate)	$N_3O_8C_{15}H_{19}$	32B	1,10–12
89971	93161	14039–08–8	Urea, 3-(1-adamantyl)-1-(2-fluoroethyl)-1-nitroso-	$N_3O_2FC_{13}H_{20}$	20	1, 12
89972	94100	488–41–5	Mannitol, 1,6-dibromo-1,6-dideoxy-, D-	$O_4Br_2C_6H_{12}$	732A	1, 12
89973	94600	30628–51–4	Camptothecin	$N_2O_4C_{20}H_{16}$	501A	1, 12
89974	403144+	—	Colchicamide	$N_2O_5C_{21}H_{24}$	21I	1, 12
89975	409962	154–93–8	Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (BCNU)	$N_3O_2Cl_2C_5H_9$	20	1, 4–6, 12
89976	529064+	7433–43–4	Urea, 1-hydroxy-1-methyl-	$N_2O_2C_2H_6$	373C	1, 12

*NSC-740 is used as a standard and the test compounds are rated accordingly.

†Most of the compounds were supplied by Drug Research and Development (DR&D) (formerly the Cancer Chemotherapy National Service Center), NCI. "P" following a code number indicates that the compound was purchased by DR&D. The source of each compound is coded as follows:

Code	*Source*	*Code*	*Source*
2	Dr. N. O. Clinton Director, Research Administration Sterling-Winthrop Research Institute Rensselaer, NY	9	Dr. John A. Derden, Jr. Research Department Union Carbide Chemicals Co. South Charleston, WVa
4P	Merck, Sharp and Dohme Research Laboratories Rahway, NJ	11P	Aldrich Chemical Co. 2369 W 29th St Milwaukee, Wisc
6C	Dr. Joseph Lein Microbiological Research Bristol Laboratories Syracuse, NY	20	Dr. John A. Montgomery Head, Organic Chemistry Division Southern Research Institute Birmingham, Ala
7P	California Corporation for Biochemical Research 3625 Medford St Los Angeles, Calif	21I	Dr. M. J. Shear National Cancer Institute, NIH Bethesda, Md

Code	Source
27C	Dr. John Ehrlich Laboratory Director in Antibiotic Research Parke, Davis and Co. Detroit, Mich
29A	Mr. John L. Davenport Charles Pfizer and Co. Maywood, NJ
32	Dr. Bernard R. Baker Department of Chemistry Stanford Research Institute Menlo Park, Calif
32B	Dr. Leon Goodman, Chairman Bio-Organic Chemistry Department Stanford Research Institute Menlo Park, Calif
35 35D	Dr. Paul W. O'Connell Biological Screening Office The Upjohn Co. Kalamazoo, Mich
49P	Eastman Kodak Co. Rochester, NY
51D	Dr. Ludwig F. Audrieth Noyes Laboratory University of Illinois Urbana, Ill
52	Miss Barbara Stearns Research Associate Division of Medicinal Chemistry Squibb Institute for Medical Research New Brunswick, NJ
57A	Dr. Benjamin Prescott National Institute of Allergy and Infectious Diseases, NIH Bethesda, Md
62A	Prof. Roland K. Robins Department of Chemistry Arizona State University Tempe, Ariz
126C	Dr. Carl Henze Sandoz Pharmaceuticals Division of Sandoz, Inc. Hanover, NJ
209A	Prof. Stanley Kirschner Department of Chemistry Wayne State University Detroit, Mich
213B	Mr. J. L. Everett, F.R.I.C. Chester Beatty Research Institute Fulham Road London, SW 3, England
217A	Dr. W. E. Scott Hoffman-La Roche, Inc. Nutley, NJ
217P	Hoffman-La Roche, Inc. Nutley, NJ
229A	Dr. Andrew Tomcufcik Cancer Chemotherapy Group Organic Chemical Research Section Lederle Laboratories Pearl River, NY
233D	Dr. S. S. Berkulis Director, Microbiological Research CIBA Pharmaceutical Co. Division of CIBA Corp. Summit, NJ
233B	Dr. Prosper Loustalot CIBA Limited Basle, Switzerland
254A	Dr. J. Schmutz Research Institute Dr. A. Wander S. A. Berne, Switzerland
261A	Dr. C. C. Cheng Head, Cancer Chemotherapy Section Midwest Research Institute Kansas City, Mo
265A	Dr. Herman Gershon Director, Biochemical Research Boyce Thompson Institute for Plant Research 1086 North Broadway Yonkers, NY
285A	Dr. Carl T. Bahner Department of Chemistry Carson-Newman College Jefferson City, Tenn
304B	Dr. H. S. Anker University of Chicago Department of Biochemistry 947 E 58th St Chicago, Ill
373	Sloan-Kettering Institute for Cancer Research 410 E 68th St New York, NY
431B	Dr. H. P. K. Agersborg, Jr. Clinical Physiologist Wyeth Laboratories Philadelphia, Pa
501A	Dr. Monroe E. Wall Research Triangle Institute P.O. Box 490 Durham, NC
613A	Dr. Orrie M. Friedman Project Officer Collaborative Research, Inc. Waltham, Mass
732A	Dr. L. Hamberger, Director Hungarian Trading Co. for Pharmaceutical Products Medimpex, Budapest Budapest, 5 Hungary

TABLE 1.—Relative effectiveness of compounds in increasing the survival time of mice with advanced lenkemia L1210; se treatment, daily to death

TABLE 1.—Relative effectiveness of compounds in increasing the survival time of mice with advanced leukemia L1210; sc treatment, daily to death

NSC No.	Compound name	Molecular formula	Expt No.	Optimal daily dose of test compound (mg/kg)	Day of treatment initiation	Median survival time (days)			Relative increase in median survival (methotrexate increase equals 100)
						Test compound	Methotrexate standard	Controls	
1. Alkylating agents									
18269	Acetamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis-	$N_4O_4C_{14}H_{18}$	DL-526	1.08	7	23.5	28	11	74
83290	2,3-Butanediol, 1,4-bis[(2-chloroethyl)-amino]-, dihydrochloride, DL-	$N_2O_2Cl_2C_8H_{18}$·2 HCl	DL-545	23.0	6	15	20	8	58
18274	Butyramide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis-	$N_4O_4C_{22}H_{24}$	DL-584	8.40	6	16.5	25.5	9	45
70806	1,3-Propanediamine, *N,N'*-bis(2-chloroethyl)-, dihydrochloride	$N_2Cl_2C_7H_{16}$·2 HCl	DL-545	46.7	6	13.5	20	8	45
			DL-555	80.0	5	13.5	23	9	32
81159	2,3-Butanediol, 1,4-bis[(*meso*-2-chloro-1-methylethyl) [or(*meso*-2-chloropropyl)]amino]-, dihydrochloride (isomer B), *meso*-	$N_2O_2Cl_2C_{10}H_{22}$·2 HCl	DL-555	7.50	5	13	23	9	28
83083	*meso*-2,3-Butanediol, 1,4-bis[(*dl*-2-chloro-1-methylethyl) [or(*dl*-2-chloropropyl)]amino]-, dihydrochloride	$N_2O_2Cl_2C_{10}H_{22}$·2HCl	DL-596	10.0	6	14	27	9	27
18270	*p*-Benzoquinone, 2,5-bis(1-aziridinyl)-3,6-diethoxy-	$N_2O_4C_{14}H_{18}$	DL-536	5.00	8	15	27.5	11	24
			DL-541	5.00	7	13	22	11	18
3052	1,9-Nonanediol, dimethanesulfonate (nonane)	$O_6S_2C_{11}H_{24}$	DL-590	130	5	11	22	8	21
65005	Adenine, 9-[2-[bis(2-chloroethyl)amino]-ethyl]-, dihydrochloride, monohydrate	$N_6Cl_2C_{11}H_{15}$·2 HCl ·HOH	DL-550	14.0	5	11	24.5	8	18
			DL-556	15.0	5	10	21	8.5	12
68303	1,5-Pentanediamine, *N,N'*-bis(2-chloroethyl)-, dihydrochloride	$N_2Cl_2C_9H_{20}$·2 HCl	DL-607	400†	6	11†	22.5	10	8†
70631	Glutamic acid, *N*-[bis(2-chloroethyl)-carbamoyl]-, diethyl ester, L-	$N_2O_5Cl_2C_{14}H_{24}$	DL-550	500†	5	9†	24.5	8	6†
42343	Propionic acid, 3-[*o*-[bis(2-chloroethyl)-amino]phenoxy]-	$NO_3Cl_2C_{13}H_{17}$	DL-564	150†	5	9†	23	8	6†
			DL-555	(30.0†)	5	8†	23	9	0†
51915	Cyclohexanecarboxamide, *N,N'*-[3,6-bis-(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]-bis-	$N_4O_4C_{24}H_{32}$	DL-526	(1388†)	7	11†	28	11	0†

TABLE 1.—Relative effectiveness of compounds in increasing the survival time of mice with advanced leukemia L1210; sc treatment, daily to death—Continued

NSC No.	Compound name	Molecular formula	Expt No.	Optimal daily dose of test compound (mg/kg)	Day of treatment initiation	Median survival time (days)			Relative increase in median survival (methotrexate increase equals 100)
						Test compound	Methotrexate standard	Controls	
44426	Acetic acid, [*p*-[bis(2-chloroethyl)amino]-phenoxy]-, ethyl ester	$NO_3Cl_2C_{14}H_{20}$	DL-584	(20–5.0)	6	9	25.5	9	0
42330	Glucopyranose, 6-[(2-chloroethyl)methylamino]-6-deoxy-, hydrochloride, D-	$NO_5ClC_9H_{18} \cdot HCl$	DL-500	(300†)	7	9.5†	21	10	0†
			DL-514	(360†)	7	9†	20	9	0†
	2. Imidazole carboxamide derivatives								
82196	Imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]-	$N_6OCl_2C_6H_{11}$	DL-556	50.0	5	30.5	21	8.5	176
87982	Imidazole-4-carboxylic acid, 5-(3,3-dimethyl-1-triazeno)-, methyl ester	$N_5O_2C_7H_{11}$	DL-536	108 †	8	17.5†	27.5	11	39†
45388	Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-	$N_6OC_6H_{10}$	DL-530	1388	6	14	27.5	9	27
			DL-521	833	7	13.5	18	9	50
	3. Nitrosourea derivatives								
88104	Urea, 3-2-chlorocyclohexyl)-1-(2-chloroethyl)-1-nitroso-, *trans*-	$N_3O_2Cl_2C_9H_{15}$	DL-564	11.3*	5	>53.5*	23	8	>303*
			DL-568	14.0*	6	32*	24	9.5	155*
409962	Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (BCNU)	$N_3O_2Cl_2C_5H_9$	DL-585	5.00	6	64	29.5	10	276
			DL-499	5.00	6	55	27	9.5	260
			DL-568	5.00	6	35	24	9.5	175
47547	Urea, 1-(2-chloroethyl)-1-nitroso-	$N_3O_2ClC_3H_6$	DL-499	1.80	6	50	27	9.5	231
79037	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-(CCNU)	$N_3O_2ClC_9H_{16}$	DL-585	14.0	6	56	29.5	10	235
			DL-568	8.40*	6	40*	24	9.5	210*
87974	Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso-	$N_3O_2FC_9H_{16}$	DL-556	15.0	5	33.5	21	8.5	208
			DL-568	14.0	6	33	24	9.5	162
86056	Urea, 3-(1-adamantyl)-1-(2-chloroethyl)-1-nitroso-	$N_3O_2ClC_{13}H_{20}$	DL-607	50.0	6	32.5	22.5	10	180
93161	Urea, 3-(1-adamantyl)-1-(2-fluoroethyl)-1-nitroso-	$N_3O_2FC_{13}H_{20}$	DL-584	65.0	6	35	25.5	9	157
88106	Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso-	$N_3O_2ClC_{10}H_{16}$	DL-556	30.0	5	24.5	21	8.5	128
91741	Urea, 1-(2-chloroethyl)-1-nitroso-3-(2,6-xylyl)-	$N_3O_2ClC_{11}H_{14}$	DL-550	65.0	5	27	24.5	8	115

91741	Urea, 1-(2-chloroethyl)-1-nitroso-3-(2,6-xylyl)-	$N_3O_2ClC_{11}H_{14}$	DL-550	65.0	5	27	24.5	8	115
89207	Urea, 3-(*p*-acetylphenyl)-1-(2-chloroethyl)-1-nitroso-	$N_3O_3ClC_{11}H_{12}$	DL-584	65.0	6	19	25.5	9	60
4. Other urea derivatives									
529064	Urea, 1-hydroxy-1-methyl-	$N_2O_2C_2H_6$	DL-514	360	7	13.5	20	9	40
			DL-500	300†	7	14†	21	10	36†
50840	Urea, 1-ethyl-1-hydroxy-	$N_2O_2C_3H_8$	DL-496	375	7	15.5	29	12	20
56054	Pseudourea, 2, 2′-(9,10-anthrylenedimethylene)bis[2-thio-, dihydrochloride, dihydrate	$N_4S_2C_{18}H_{20}\cdot 2\ HCl \cdot 2\ HOH$	DL-514	39.0	7	9.5	20	9	4
			DL-500	(180.0†)	7	9†	21	10	0†
77517	Urea, [α-(2-methylhydrazino)-*p*-toluoyl]-, monohydrobromide	$N_4O_2C_{10}H_{14}\cdot HBr$	DL-556	200†	5	9†	21	8.5	4†
5. Pyrimidine derivatives									
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytarabine hydrochloride)	$N_3O_5C_9H_{13}\cdot HCl$	DL-481	39.0	7	47	24.5	11	267
			DL-483	39.0	7	52.5	22.5	11	360
			DL-544	20.0	5	52	29	10	221
			DL-523	23.0	7	52	28.5	10	227
93150	Cytosine, 1-β-D-arabinofuranosyl-, 2′,3′,5′-triacetate	$N_3O_8C_{15}H_{19}$	DL-544	80.0	5	36	29	10	136
31712	Orotic acid, 5-fluoro-, monohydrate	$N_2O_4FC_5H_3\cdot HOH$	DL-505	40.0	6	15	24.5	8.5	40
64333	Orotic acid, 5-fluoro-, methyl ester	$N_2O_4FC_6H_5$	DL-505	20.0	6	14	24.5	8.5	33
65987	Pyrimidine, 2,4,5-triamino-	$N_5C_4H_7$	DL-484	108	9	14	26.5	13	7
80362	2,5-Pyridinedicarboxanilide, 4′,4″-bis-(1,4,5,6-tetrahydro-2-pyrimidinyl)-, dihydrochloride, dihydrate	$N_7O_2C_{17}H_{27}\cdot 2\ HCl \cdot 2\ HOH$	DL-584	23.0–3.0	6	9	25.5	9	0
6. Purine derivatives									
76955	9H-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2′,3′,5′-tributyrate	$N_5O_7SC_{23}H_{33}$	DL-545	65.0	6	14	20	8	50
1895	1,2,4-Triazolidine, 3,5-diimino-(guanazole)	$N_5C_2H_5$	DL-536	2000	8	16.5	27.5	11	33
			DL-541	2000	7	14	22	11	27
49928	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α′-(hydroxymethyl)-, monohydrochloride	$N_5O_4C_{12}H_{13}\cdot HCl$	DL-521	65.0	7	12	18	9	33

TABLE 1.—Relative effectiveness of compounds in increasing the survival time of mice with advanced leukemia L1210; sc treatment, daily to death—Continued

NSC No.	Compound name	Molecular formula	Expt No.	Optimal daily dose of test compound (mg/kg)	Day of treatment initiation	Median survival time (days)			Relative increase in median survival (methotrexate increase equals 100)
						Test compound	Methotrexate standard	Controls	
40774	9*H*-Purine, 6-(methylthio)-9-β-D-ribofuranosyl-, dihydrate	$N_4O_4SC_{11}H_{14}$ • 2 HOH	DL-502	108	6	13	21.5	9	32
			DL-498	108	7	14	23.5	10	29
70088	Purine-6-thiol, disodium salt, compd. with bismuth oxide (Bi O) (3:1), trihydrate	$N_4SC_5H_4$ • Na salt • ⅓(Bi O) • 3 HOH	DL-555	60.0†	5	13†	23	9	28†
76954	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2′,3′,5′-tris(*p*-chlorobenzoate)	$N_5O_7SCl_3C_{31}H_{22}$	DL-564	200†	5	12†	23	8	27†
77556	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2′,3′,5′-tripropionate	$N_5O_7SC_{19}H_{25}$	DL-533	39.0†	8	14.5†	27	11	21†
22837	Guanosine, 2′-deoxy-	$N_5O_4C_{10}H_{13}$	DL-514	(1000–130)	7	9	20	9	0
52385	Purine, 2-amino-6-[[6-chloro-2-(ethylthio)-4-pyrimidinyl]-thio]-	$N_7S_2ClC_{11}H_{10}$	DL-496	(400†)	7	12†	29	12	0†
	7. Antibiotics								
31083	Isocoumarin, 4-(2-aminopropionamido)-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl- (actinobolin)	$N_2O_6C_{12}H_{20}$	DL-484	833	9	17	26.5	13	29
69856	Neocarzinostatin, crystalline antibiotic	Unknown	DL-514	500	7	11	20	9	18
			DL-502	400†	6	10†	21.5	9	8†
37917	Streptozotocin (mixture, lot 4621)	$N_3O_{12}C_{14}H_{27}$	DL-550	300	5	9	24.5	8	6
	8. Other compounds								
69185	*p*-Cymene-2-sulfonic acid, 5-hydroxy-, compd. with 1,1′-[methylethanediylidene)dinitrilo]diguanidine (2:1)	$O_4SC_{10}H_{14}$ • ½ $N_8C_3H_{12}$	DL-556	250	5	12.5	21	8.5	32
13002	Acridine, 9-[*p*-(dimethylamino)anilino]-	$N_3C_{21}H_{19}$	DL-533	720†	8	15.5†	27	11	28†
60542	Ethane, 1,2-dimethoxy-	$O_2C_4H_{10}$	DL-500	1000	7	13	21	10	27
66796	Cyclopentanecarboxylic acid, 1-(2-aminoacetamide)-, monohydrochloride	$N_2O_3C_8H_{14}$ • HCl	DL-499	253	6	15	27	9.5	21
94600	Camptothecin	$N_2O_4C_{20}H_{16}$	DL-520	1.00†	7	11†	18	9	22†

94600	Camptothecin	$N_2O_4C_{20}H_{16}$	DL-520	1.00†	7	11†	18	9	22†
			DL-526	1.80	7	13.5	28	11	14
83693	Butyric acid, 4-[*p*-3,3-dimethyl-1-triazeno)phenyl]-, hydrazide	$N_5OC_{12}H_{19}$	DL-536	39.0	8	13	27.5	11	12
50164	Colchicine, demethyl-	$NO_6C_{21}H_{23}$	DL-541	7.50	7	12	22	11	9
403144	Colchicamide	$N_2O_5C_{21}H_{24}$	DL-541	16.0	7	12	22	11	9
58404	Glycine, *N*-(diazoacetyl)-, hydrazide	$N_5O_2C_4H_7$	DL-484	833	9	14	26.5	13	7
42076	Podophyllotoxin, 4,6-*O*-benzylidene-*β*-D-glucoside	$O_{13}C_{28}H_{28}$	DL-521	833	7	10.5	18	9	5
90440	Leucine, 5,5,5-trifluoro-, DL-	$NO_2F_3C_6H_{10}$	DL-496	2000†	7	13†	29	12	5
80087	p-Toluidine, *α*-inden-1-ylidene-*N*,*N*-dimethyl-	$NC_{18}H_{17}$	DL-596	833	6	10	27	9	5
			DL-590	(300†)	5	8†	22	8	0†
90439	Valine, 4,4,4-trifluoro-, DL-	$NO_2F_3C_5H_8$	DL-496	0.94	7	12.5	29	12	2
87206	6*H*-Pyrido[4,3-*b*]carbazole, 5-methyl-	$N_2C_{18}H_{12}$	DL-514	(280†)	7	9†	20	9	0†
			DL-524	(20.0†)	6	9.5	27	10	0
74944	8-Quinolinol, 5-fluoro-	$NOFC_9H_6$	DL-521	(300†)	7	9†	18	9	0†
49271	2(1*H*)-Pyridone, 1,5-dihydroxy-6-methyl-	$NO_3C_6H_7$	DL-526	(500†)	7	11†	28	11	0†
94100	Mannitol, 1,6-dibromo-1,6-dideoxy-, D-	$O_4Br_2C_6H_{12}$	DL-530	(500†)	6	9	27.5	9	0†

*† Instances in which optimal daily dose may be outside the range employed. *See* Materials and Methods.

TABLE 2.—Influence of route of drug administration and schedule of treatment on the activity of 6-methylmercaptopurine riboside (NSC-40774) against advanced leukemia L1210 and in normal mice

Treatment	Optimal daily dose (mg/kg)	Leukemic mice: Median survival time (days)	Leukemic mice: Increase over controls (%)	Normal mice: Median survival time (days)	Normal mice: No. of 25-day survivors
Route*					
sc	108	14	40	15	0/8
ip	65.0‡	11	10	16.5	0/8
iv	39.0‡	10.5	5	>25	8/8
oral	300	12.5	25	14	0/8
Methotrexate (standard) sc	0.65	23.5	135	>25	8/8
Untreated controls		10			
Schedule†					
Twice daily	39.0	10	11	15	0/8
Daily	108	13	44	14	0/8
Every 2 days	108‡	10‡	11‡	19	0/8
Every 4 days	300	11	22	8	0/8
Single injection	300	11	22	>26	8/8
Methotrexate (standard) daily	1.08	21.5	139	>26	8/8
Untreated controls		9			

*Expt DL-498: 8 BDF$_1$ male mice, 19–25 g per group; treatment started Day 7.

†Expt DL-502: 8 BDF$_1$ male mice, 18–24 g per group; sc treatment started Day 6.

‡Optimal dose may be higher than any employed.

TABLE 3.—Influence of treatment schedule on antileukemic activity of 6-methylmercaptopurine riboside (NSC-40774) administered orally or ip in mice with early leukemia L1210*

Treatment schedule	Oral treatment: Optimal dose (mg/kg)	Oral treatment: Median survival time (days)	Oral treatment: Increase over controls (%)	Ip treatment: Optimal dose (mg/kg)	Ip treatment: Median survival time (days)	Ip treatment: Increase over controls (%)
Daily	39.0	15	50	39.0	12	20
Every 3 days	108	16	60	103	16	60
Every 7 days	300	21	110	180	17	70
Single injection	500	17.5	75	180	16.5	65
Methotrexate (standard) daily	1.80	28	180			
Untreated controls		10				

*Expt DL-618: 8 BDF$_1$ male mice, 20–30 g per group; splenic inoculum; treatment started Day 3.

TABLE 4.—Influence of treatment schedule on the activity of urea, 1-(2-chloroethyl)-1-nitroso- (NSC-47547) and BCNU (NSC-409962) against advanced leukemia L1210 and in mice without tumors*

Treatment schedule	Dose (mg/kg)	Leukemic mice				Mice without tumors	
		NSC-47547		NSC-409962		No. of 80-day survivors	
		Median survival time † (days)	Increase over controls (%)	Median survival time † (days)	Increase over controls (%)	NSC-47547	NSC-409962
Daily	14.0	—	—	26	173	—	0/8
	8.40	—	—	41	331	—	0/8
	5.00	29.5	210	55	478	0/8	0/8
	3.00	44	363	31.5 (1)	231	0/8	3/8
	1.80	50	426	14	47	0/8	7/8
	1.08	26	173	—	—	0/8	—
	0.65	16	68	—	—	5/8	—
Every 7 days	23.0	14.5	52	60	531	0/8	0/8
	14.0	24.5	157	63	563	0/8	1/8
	8.40	27.5 (1)	189	24 (1)	152	1/8	6/8
	5.00	19	100	12.5	31	8/8	7/8
	3.00	12	26	—	—	8/8	—
Single injection	65.0	—	—	33 (2)	247	—	0/8
	39.0	12	26	60 (3)	531	0/8	5/8
	23.0	12	26	36 (1)	278	0/8	8/8
	14.0	17	78	24.5 (2)	157	1/8	8/8
	8.40	17	78	16	68	6/8	8/8
	5.00	15	57	—	—	8/8	—
Methotrexate (standard) daily‡	0.65						
Untreated controls§							

*Expt DL-499: 8 BDF_1 male mice, 19–25 g per group; sc treatment from Day 6.
†Numbers in parentheses are 80-day survivors from a group of 8 leukemic mice.
‡Median survival time = 27 days.
§Median survival time = 9.5 days.

TABLE 5.—Effect of treatment schedule on the activity of BCNU (NSC-409962) and CCNU (NSC-79037) against advanced leukemia L1210 and in normal mice*

Treatment schedule	Dose (mg/kg)	Leukemic mice				Normal mice	
		NSC-409962		NSC-79037		No. of 75-day survivors	
		Median survival time† (days)	Increase over controls (%)	Median survival time (days)	Increase over controls (%)	NSC-409962	NSC-79037
Daily	23.0	—	—	26.5	165	—	0/8
	14.0	28.5	185	56	460	0/8	0/8
	8.40	45.5	355	31.5 (1)	215	0/8	8/8
	5.00	64	540	12	20	0/8	8/8
	3.00	24	140	11	10	8/8	7/8
	1.80	11	10	—	—	3/8	—
Every 7 days	65.0	—	—	33	230	—	0/8
	39.0	31.5	215	>75 (8)	>650	0/8	8/8
	23.0	64.5	545	17 (3)	70	1/8	4/8
	14.0	>75 (5)	>630	16.5	65	8/8	8/8
	8.40	21 (1)	110	10	0	7/8	7/8
	5.00	12	20	—	—	8/8	—
Single injection	108	—	—	>75 (7)	>650	—	8/8
	65.0	13.5 (1)	35	35.5 (3)	255	5/8	7/8
	39.0	>34.5 (4)	>445	29.5	195	3/8	6/8
	23.0	37 (2)	270	15	50	7/8	8/8
	14.0	26 (1)	160	12	20	8/8	8/8
	8.40	17	70	—	—	8/8	—
Methotrexate (standard) daily‡	1.08						
Untreated controls§							

*Expt DL-585: BDF$_1$ male mice, 22–30 g per group; sc treatment from Day 6.
†Numbers in parentheses are 75-day survivors from a group of 10 leukemic mice.
‡Median survival time = 29.5 days.
§Median survival time = 10 days.

TABLE 6.—Effect of sc and oral treatment on the activity of several urea derivatives against advanced leukemia L1210*

Agent (NSC No.)	Treatment route	Optimal daily dose (mg/kg)	Leukemic mice: Median survival time (days)	Leukemic mice: Increase over controls (%)	Leukemic mice: No. of 67-day survivors
Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (409962)	sc	5.00	35	268	0/8
	oral	5.00	49.5	421	0/8
Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (79037)	sc	8.40†	40†	322†	0/8
	oral	8.40	42.5	347	1/8
Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso- (88106)	sc	39.0	47.5	400	0/8
	oral	39.0	51.5	442	3/8
Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso- (87974)	sc	14.0	33	247	1/8
	oral	14.0	>67	>605	6/8
Urea, 3-2-chlorocyclohexyl)-1-(2-chloroethyl)-1-nitroso-, *trans-* (88104)	sc	14.0†	32†	236†	0/8
	oral	23.0†	31†	226†	0/8
Methotrexate (standard)	sc	0.65	24		
Untreated controls‡					

*Expt DL-568: BDF_1 male mice, 19–29 g per group; daily treatment from Day 6.
†The optimal dose may be lower than any employed.
‡Median survival time = 9.5 days.

TABLE 7.—Influence of treatment schedule on the activity of cytosine arabinoside (ara-C; NSC-63878) against advanced leukemia L1210*

Treatment schedule	Optimal dose (mg/kg/injection)	Leukemic mice: Median survival time (days)	Leukemic mice: No. of 90-day survivors	Leukemic mice: Increase over controls (%)	Normal mice: Days of death (range)	Normal mice: No. of 90-day survivors
Daily, Day 7 to death	39.0	52.5	0/8	377	23–57	0/8
Twice daily	23.0	57.5	0/8	422	23	7/8
4 times daily	8.40	76	1/8	590	—	8/8
Every 2 days	300	64	0/8	481	—	8/8
Every 4 days	833	56	0/8	409	33	6/8
Single injection	1388	18.5	0/8	68	—	8/8
Methotrexate (standard) daily	1.08	22.5				
Untreated controls†						

*Expt DL-483: BDF_1 male mice, 19–24 g per group; sc treatment from Day 7.
†Median survival time = 11 days.

TABLE 8.—Influence of route of administration on the activity of cytosine arabinoside (ara-C; NSC-63878) against advanced leukemia L1210 and normal mice*

Treatment route	Leukemic mice			Normal mice	
	Optimal daily dose (mg/kg)	Median survival time (days)†	Increase over controls (%)	Days of death (range)	No. of 84-day survivors
sc	39.0	47 (2)	327	46	7/8
ip	23.0	76 (2)	591	84	7/8
iv	39.0	44.5	304		8/8
oral	65.0	25.5	131	23–27	6/8
oral with fasting	65.0	27	145	23–62	4/8
Methotrexate (standard) sc	0.65	24.5			
Untreated controls‡					

*Expt DL-481: CDBA male mice, 19–27 g per group; daily treatment from Day 7.
†Numbers in parentheses are 84-day survivors from a group of 8 leukemic mice.
‡Median survival time = 11 days.

TABLE 9.—Influence of treatment schedule and route of administration on the activity of cytosine arabinoside (ara-C; NSC-63878) against advanced leukemia L1210 and normal mice*

Treatment schedule	Treatment route	Optimal daily dose (mg/kg)	Leukemic mice			Normal mice	
			Median survival time (days)	No. of 84-day survivors	Increase over controls (%)	Days of death (range)	No. of 84-day survivors
4 times daily	sc	8.40	74	3/8	640	27–29	5/8
	oral	14.0	34	0/8	240	13–20	3/8
Twice daily	sc	23.0	>74	4/8	>640	—	8/8
	oral	65.0	32	0/8	220	19–49	5/8
Daily	sc	23.0	52	1/8	420	—	8/8
	oral	108	27	0/8	170	17–32	2/8
Methotrexate (standard) daily	sc	0.85	28.5				
Untreated controls†							

*Expt DL-523: CDBA male mice, 19–27 g per group; treatment from Day 7.
†Median survival time = 10 days.

TABLE 10.—Influence of route of administration on the activity of cytosine arabinoside (ara-C; NSC-63878) compared to cytosine arabinoside triacetate (NSC-93150) against advanced leukemia L1210*

NSC No.	Daily dose (mg/kg)	Route of treatment: Oral — Median survival time (days)	Oral — Increase over controls (%)	Sc — Median survival time (days)	Sc — Increase over controls (%)
63878	320	14.5	45	—	—
	160	31.5	210	—	—
	80.0	28.5	185	14	40
	40.0	20.5	165	23	130
	20.0	23	130	52 (1)†	420
	10.0	—	—	26.5	165
	5.00	—	—	26	160
93150	640	14	40	—	—
	320	32	220	13.5	35
	160	26	160	22.5	125
	80.0	27	170	36	260
	40.0	25.5	155	36	260
	20.0	22	120	29	190
Methotrexate (standard) sc	1.08			29	
Untreated controls‡					

*Expt DL-544: BDF_1 male mice, 19–29 g per group; daily treatment from Day 5.
†54-day survivor from a group of 3 leukemic mice.
‡Median survival time = 10 days.

TABLE 11.—Influence of treatment schedule on the activity of cytosine arabinoside (ara-C; NSC-63878) and cytosine arabinoside triacetate (NSC-93150) given orally against leukemia L1210*

Treatment schedule	NSC-63878: Dose range (mg/kg/injection)	NSC-63878: Optimal dose (mg/kg/injection)	NSC-63878: Median survival time (days)	NSC-63878: Increase over controls (%)	NSC-93150: Dose range (mg/kg/injection)	NSC-93150: Optimal dose (mg/kg/injection)	NSC-93150: Median survival time (days)	NSC-93150: Increase over controls (%)
Day 1 only	3855–833	1388	14	55	5088–1099	3053	13	44
Every 3 hrs, Day 1 only	108–14	65.0	15	67	143–18	143	13	44
Daily, Days 1–9	300–65	108	14.5	61	396–86	396†	16†	78
Days 1, 5, and 9	2313–500	833	21	133	3053–660	1099	18.5	106
Every 3 hrs, Days 1, 5, and 9	65–14	65.0	22.5 (1)‡	150	86–18	51.0	16.5	84
Untreated controls§								

*Expt D-1342: BDF_1 female mice, 17–22 g per group; ip tumor inoculation (10^5 ascites cells), oral treatment.
†The optimal dose may be higher than any employed.
‡38-day survivor from a group of 8 leukemic mice.
§Median survival time = 9 days.

TABLE 12.—Treatment of advanced leukemia L1210 in mice: summary of 32 experiments

Expt No. DL-481 [1]

NSC No.	Compound, molecular formula, and vehicle [‡]	Treatment route	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 7 through 10	11 through 15	16 through 20	21 through 25	26 through 30	31 through 35	36 through 40	41 through 45	46 through 50	51 through 55	56 through 60	61 through 84
					(Mice with leukemia L1210)											
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-(methotrexate)	sc	3.00	15.5		4	4									
			1.80	19			6	1		1						
			1.08	22		1	2	5								
			0.65	24.5		3		1	3	1						
			0.39	16.5		3	3	2								
	$N_8O_5C_{20}H_{22}$															
	B															
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside; ara-C)	sc	65.0	19		2	3	2	1							
			39.0	47			1		1	2			(2 survivors Day 84)			2
			23.0	39.5				1	2		1	1	(2 survivors Day 84)			1
			14.0	27				1	5							2
	$N_3O_5C_9H_{13} \cdot HCl$		8.40	35.5				2	1	1	1		(2 survivors Day 84)			1
	A	ip	39.0	30				1	4	1			1	(1 survivor Day 84)		
			23.0	76					1				1	(2 survivors Day 84)		4
			14.0	33		1			1	4	1					1
			8.40	29				1	3	1	1		(1 survivor Day 84)		1	
			5.00	26.5				2	5	1						
		iv	39.0	44.5				1	2			1	1	1	1	1
			23.0	32				2	1	3				1	1	
			14.0	25.5			1	3	1	1			1	(1 survivor Day 84)		
			8.40	19		2	3		2	1						
			5.00	19.5		2	2	3	1							
		oral	108	24.5		1		3	3	1						
			65.0	25.5				4	2	1						1
			39.0	24.5		1		3	2	2						
			23.0	25				4	3	1						
			14.0	22.5			1	5	2							
		oral, with fasting	108	24				7			1					
			65.0	27				3	4							1
			39.0	22			3	2	2		1					
			23.0	22.5			3	4	1							
			14.0	18		2	4	1		1						
	Controls, expt inoc		—	11		7	1									
	Controls, expt inoc		—	11		8										
	Controls, 1/10 expt inoc		—	13.5		4										
	Controls, 1/100 expt inoc		—	—		1								(3 survivors Day 84)		
	Retransplant recipients		—	10 (from Day 7)			4									
	Untreated without tumor		—	—										(6 survivors Day 84)		
					(Mice without tumors)											
740	Glutamic acid, *N*-[*p*-	sc	3.00	19			3	3	3	1						

					(Mice without tumors)								
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]-benzoyl]- (methotrexate)	sc	3.00	18	3	2	2	1					
			1.80	22		1	7						
			1.08	29.5				5	2				(1 survivor Day 84)
			0.65										(8 survivors Day 84)
			0.39										(8 survivors Day 84)
	$N_8O_6C_{20}H_{22}$												
	B												
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside; ara-C)	sc	65.0	37.5				2	1	2	1		2
			39.0									1	(7 survivors Day 84)
			23.0										(8 survivors Day 84)
			14.0										(8 survivors Day 84)
	$N_3O_4C_9H_{13}$ • HCl		8.40										(8 survivors Day 84)
	A	ip	39.0				3				1		(4 survivors Day 84)
			23.0										(7 survivors Day 84) 1
			14.0										(8 survivors Day 84)
			8.40										(8 survivors Day 84)
			5.00										(8 survivors Day 84)
		iv	39.0										(8 survivors Day 84)
			23.0		1	1	1		1				(5 survivors Day 84)
			14.0										(8 survivors Day 84)
			8.40										(8 survivors Day 84)
			5.00					1					(7 survivors Day 84)
		oral	108	25.5	1	2	1	2					(2 survivors Day 84)
			65.0				1	1					(6 survivors Day 84)
			39.0										(8 survivors Day 84)
			23.0		1	1							(6 survivors Day 84)
			14.0		1		1						(5 survivors Day 84) 1
		oral, with fasting	108			1		2				1	(4 survivors Day 84)
			65.0				3						(4 survivors Day 84) 1
			39.0			1		1					(6 survivors Day 84)
			23.0										(8 survivors Day 84)
			14.0				1			1			(6 survivors Day 84)

[1] CDBA male mice, 19–27 g per group; experimental inoc, 12,840,000 cells/mouse; daily treatment begun Day 7.

‡The vehicle used for each compound is coded as follows:

Code	*Vehicle*
A	Distilled water
B	2%sodium bicarbonate solution
C	0.5% methyl cellulose
D	0.85% saline solution
E	Dilute sodium hydroxide solution
F	Carboxymethylcellulose

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-483 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 7 10	11 15	16 20	21 25	26 30	31 through 35	36 40	41 45	46 50	51 55	56 60	61 90
					(Mice with leukemia L1210)											
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-(methotrexate)	Daily	3.00	19.5			4	4								
			1.80	22.5			3	4	1							
			1.08	22.5				8								
			0.65	13		8										
			0.39	13		6	1		1							
	$N_8O_6C_{20}H_{22}$		0.23	13		7		1								
	B															
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside)	Daily	65.0	24				6	2							
			39.0	52.5				1	1	1			1		2	2
			23.0	48.5			1	2	1							4
			14.0	30				2	2	3						1
	$N_3O_5C_9H_{13}\cdot HCl$		8.40	29.5				1	3	4						
	A	Twice daily	23.0	57.5				1		2		1				4
			14.0	51.5					2	1		1	(1 survivor Day 90)			3
			8.40	46.5					3	1		1	1	1		2
			5.00	54				1	1			1	1			4
		4 times daily	14.0	25		1		3	4							
			8.40	76					2	1			(1 survivor Day 90)			4
			5.00	70.5												3
			3.00	58.5			1	1	1					1		4
			1.80	49.5				1			1		2	1		3
		Every 2 days	500	37.5				1	1	1	2	1		2		
			300	64					1		1					6
			180	34				1	2	3	2					
			108	50.5				2	1				1	1		3
			65.0	24.5			1	4		1			1		1	
		Every 4 days	1388	15.5		4	1		2	1						
			833	56					1	1				2	1	3
			500	40					2		2	1				3
			300	18		4		3	1							
		Single injection	2313	15.5		4	3	1								
			1388	18.5			7	1								
			833	15.5		4	4									
			500	17		3	5									
	Controls, expt inoc		—	11		8										
	Controls, expt inoc		—	11		8										
	Controls, 1/10 expt inoc		—	14		3	1									
	Controls, 1/100 expt inoc		—	17			3						(1 survivor Day 90)			
	Retransplant recipients		—	9.5 (from Day 7)		1	3									
	Untreated without tumor		—	—									(5 survivors Day 90)			
					(Mice without tumors)											

				(Mice without tumors)							
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-(methotrexate)	Daily	3.00	31		2	1	1	3	1	
			1.80								(8 survivors Day 90)
			1.08								(8 survivors Day 90)
			0.65								(8 survivors Day 90)
	$N_2O_5C_{20}H_{22}$		0.39								(8 survivors Day 90)
			0.23								(8 survivors Day 90)
	B										
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside)	Daily	65.0	28		2	1	4	1		
			39.0	43			1	1	1	2	3
			23.0								(8 survivors Day 90)
			14.0								(8 survivors Day 90)
	$N_3O_5C_9H_{13} \cdot HCl$		8.40								(8 survivors Day 90)
	A	Twice daily	23.0				1				(7 survivors Day 90)
			14.0								(8 survivors Day 90)
			8.40								(8 survivors Day 90)
			5.00								(8 survivors Day 90)
		4 times daily	14.0			6	1				(1 survivor Day 90)
			8.40								(8 survivors Day 90)
			5.00	64						(2 survivors Day 90)	1 1 4
			3.00								1 (7 survivors Day 90)
			1.80								(8 survivors Day 90)
		Every 2 days	500			1	(5 survivors Day 90)			1	1
			300								(8 survivors Day 90)
			180								1 (7 survivors Day 90)
			108			1		1		1	(5 survivors Day 90)
			65.0								(8 survivors Day 90)
		Every 4 days	1388			1	1	1			(5 survivors Day 90)
			833						2		(6 survivors Day 90)
			500								(8 survivors Day 90)
			300								(8 survivors Day 90)
		Single injection	2313		2						
			1388								(8 survivors Day 90)
			833								(8 survivors Day 90)
			500								(8 survivors Day 90)

[1]BDF_1 male mice, 19–24 g per group; experimental inoc, 8,660,000 cells/mouse; sc treatment begun Day 7.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-484 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Dose (mg/kg/ injection)	Median survival time (days)	Mortality distribution (days after tumor implantation) 9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-(methotrexate)	Daily	3.00	20										3	1	2	3	1							
			1.80	19						1				4		1		2		1		(1 survivor Day 30)			
			1.08	26.5						3						(3 survivors Day 30)					2			2	
			0.65	19						5						(1 survivor Day 30)				1			2		1
			0.39	14						7			1										1		1
	$N_8O_6C_{20}H_{22}$																								
	B																								
58404	Glycine, *N*-(diazoacetyl)-, hydrazide	Daily	833	14						7		1						1	1						
			500	13				4	4	2															
			300	13				2	4		1	3													
	$N_5O_2C_4H_7$		180	13				1	6	2		1													
	D		108	13				1	7	1			1												
65987	Pyrimidine, 2,4,5-triamino-	Daily	500	13				3	4	3															
			300	13			1	2	4	2			1												
	$N_5C_4H_7$		180	13				1	6	3															
			108	14					3	7															
	C		65.0	13				1	6	3															
31083	Isocoumarin, 4-(2-aminopropionamide)-3,4,4a,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-(actinobolin)	Daily	1388	17						1		3	2	3	1										
			833	17						3		2		1				1	3						
			500	14					2	5			1		1				1						
			300	13					7	2				1											
			180	13				2	4	3					1										
	$N_2O_6C_{13}H_{20}$	Twice	1388	15							6	1	1	2											
		daily	833	18						4				2	1	2	1								
	D		500	13.5					5	1	1								1	1	1				
			300	14					4	4	1					1									
			180	13.5				1	4	2		2	1												
	Controls, expt inoc		—	13				4	5	1															
	Controls, expt inoc		—	13				4	4	2															
	Controls, 1/10 expt inoc		—	15.5						2			1	1											
	Controls, 1/100 expt inoc		—													1						(3 survivors Day 30)			
	Retransplant recipients		—	13.5 (from Day 9)													1	1	1		1				
	Untreated without tumor		—	—																		(6 survivors Day 30)			

[1] BDF_1 male mice, 19–24 g per group; experimental inoc, 12,600,000 cells/ mouse; sc treatment begun Day 9.
‡*See* footnote (‡) on page 28.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-496 [1]

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-496 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																												
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	38	44
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]-benzoyl]-(methotrexate)	3.00	26										1					2	1				4					1		1		
		1.50	29				(1 survivor Day 44)										1	1	1						1	2		2		1		
		0.75	25											1		2	1				1		2	2		1					
		0.37	19.5						2	2		1									1	1			1	1		1				
	$N_2O_8C_{20}H_{22}$																															
	B																															
90439	Valine, 4,4,4-trifluoro-, DL-	15.0	11					5		1																						
		7.50	11					4	2																							
	$NO_2F_3C_5H_8$	3.75	12					2	2	1		1																				
		1.88	11.5					3	3																							
	A	0.94	12.5					1	2	2		1																				
90440	Leucine, 5,5,5-trifluoro-, DL-	2000†	13†					2		4																						
		1000	12						6																							
	$NO_2F_3C_6H_{10}$	500	12					1	3	1	1																					
	C																															
52385	Purine, 2-amino-6-[[6-chloro-2-(ethylthio)-4-pyrimidinyl]thio]-	640	11.5					4	2		2																					
		400	12					2	4	2																						
		250	12					2	5			1																				
	$N_7S_2ClC_{11}H_{10}$	156	12				1	1	4	2																						
		97.5	12					1	6	1																						
	C																															
50840	Urea, 1-ethyl-1-hydroxy-	500	15								1	4	2	1																		
		375	15.5								1	3	2	2																		
	$N_2O_2C_3H_8$	250	13.5						2	2	2		1	1																		
		125	12					2	3	1	2																					
	C	62.0	13					1	5	2																						
		31.0	12					1	7																							
		16.0	12					3	3	1		1																				
		8.00	13					3	4			1																				
		4.00	11					6	2																							
		2.00	12.5					3	1	2	1			1																		
		1.00	11.5					4	3	1																						
	Controls, expt inoc	—	12					3	5																							
	Controls, expt inoc	—	12					3	4	1																						
	Controls, 1/10 expt inoc	—	18.5											2			1	(1 survivor Day 44)														
	Controls, 1/100 expt inoc	—	16					1					2					(1 survivor Day 44)														
	Retransplant recipients	—	11	(from Day 7)									1		2	1																
	Untreated without tumor	—	—															(6 survivors Day 44)														

[1] BDF_1 male mice, 19–25 g per group; experimental inoc, 7,640,000 cells/mouse; daily ac treatment begun Day 7.
† No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡ *See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-498 [1]

NSC No.	Compound, molecular formula, and vehicle[‡]	Treatment route	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	(Mice with leukemia L1210)																						
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (methotrexate)	sc	3.00	18											1	5	1				1		
			1.80	19.5								1			1	1	1	1		1	2		
			1.08	22.5							(3 survivors Day 25)							2		2	1		
			0.65	23.5					1	1	(3 survivors Day 25)										2	1	
			0.39	11			2		3	1	(2 survivors Day 25)												
	$N_8O_8C_{20}H_{22}$																						
	B																						
40774	9*H*-Purine, 6-(methylthio)-9-β-D-ribofuranosyl-, dihydrate (6-methylthiopurine riboside)	sc	108	14	1						1	3	3										
			65.0	12				1	2	2	1		2										
			39.0	11				2	5	1													
			23.0	10.5				4	4														
			14.0	11				3	3		2												
	$N_4O_4SC_{11}H_{14}\cdot 2HOH$																						
		ip	65.0	11				3	2	2			1										
	A		39.0	10.5			1	3	4														
			23.0	11				3	5														
			14.0	11	1			2	2	2	1												
			8.40	11				3	4	1													
		iv	65.0	10			1	4	3														
			39.0	10.5				4	4														
			23.0	10				5	3														
			14.0	10				7		1													
			8.40	10				6	2														
		oral	300	12.5						4	4												
			180	11				3	2		2		1										
			108	11.5				3	1	1				2		1							
			65.0	11				2	4	2													
			39.0	10				5	2	1													
	Controls, expt inoc		—	10				8															
	Controls, expt inoc		—	10			3	2	2		1												
	Controls, 1/10 expt inoc		—	13						2		1		1									
	Controls, 1/100 expt inoc		—	18								1				2					1		
	Untreated without tumor		—	—														(6 survivors Day 25)					
	(Mice without tumors)																						
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-(methotrexate)	sc	3.00	22									(3 survivors Day 25)					1		4			
			1.80															1		(7 survivors Day 25)			
			1.08																	(8 survivors Day 25)			
			0.65																	(8 survivors Day 25)			
			0.39																	(8 survivors Day 25)			
	$N_8O_8C_{20}H_{22}$																						
	B																						
40774	9*H*-Purine, 6-(methylthio)-9-β-D-ribofuranosyl-	sc	108	16									5	2		1							
			65.0	17.5									1		3	2		2					

| | | |

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-499 [1]

NSC No.	Compound, molecular formula, and vehicle[2]	Treatment schedule	Dose (mg/kg/-injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 6 through 10	11 through 15	16 through 20	21 through 25	26 through 30	31 through 35	36 through 40	41 through 45	46 through 50	51 through 55	56 through 60	61 through 80
					(Mice with leukemia L1210)											
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-(methotrexate)	Daily	3.00	19.5		1	4	3								
			1.80	23			3	4	1							
			1.08	25.5			1	3	4							
			0.65	27		1		1	6							
	$N_8O_6C_{20}H_{22}$		0.39	10.5	4	2	1	1								
	B															
47547	Urea, 1-(2-chloroethyl)-1-nitroso-	Daily	5.00	29.5				3	1	2	2					
			3.00	44						1	2	2	3			
	$N_3O_2ClC_2H_6$		1.80	50				1	2				2	1	2	
			1.08	26			1	2	2	1	1	1				
	D		0.65	16	1	2	4		1							
		Single injection	39.0	12		8										
			23.0	12		7	1									
			14.0	17			8									
			8.40	17			7	1								
			5.00	15		6	2									
		Every 7 days	23.0	14.5		5	3									
			14.0	24.5		2		2	4							
			8.40	27.5			2	1	2	2						(1 survivor Day 60)
			5.00	19		3	5									
			3.00	12	1	6		1								
409962	Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (BCNU)	Daily	14.0	26			1	2	4	1						
			8.40	41						1	3	2	2			
			5.00	55									3	1	1	2
	$N_2O_2Cl_2C_5H_8$		3.00	31.5				2	2	1	1	(1 survivor Day 80)				1
			1.80	14		5	1		2							
	D															
		Single injection	65.0	33	1	2				2		(2 survivors Day 80)				1
			39.0	60	(1 survivor Day 80)			1		1			1	1		1
			23.0	36	(1 survivor Day 80)			1		3	1		1			1
			14.0	24.5			1	3	1	1		(2 survivors Day 80)				
			8.40	16		1	5	2								
		Every 7 days	23.0	60							1		1	1	1	4
			14.0	63					1				2			5
			8.40	24			4		1			(1 survivor Day 80)				2
			5.00	12.5		8										
					(Mice without tumors)											
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-	Daily	3.00	19		2	3	1	1		1					

| | | | | (Mice without tumors) | | | |

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-499—Continued

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	80
					(Mice with leukemia L1210)																	
66796	Cyclopentanecarboxylic acid, 1-(2-aminoacetamide)-, monohydrochloride	Daily	720	13							1	4	1	1	1							
			432	13.5								4	2		2							
			253	15					1			2	1		4							
			152	10			1		6	1												
			91.0	10			2	1	3	2												
	$N_3O_3C_6H_{16}$·HCl		55.0	10				2	6													
	A																					
	Controls, expt inoc		—	10				2	6													
	Controls, expt inoc		—	9				6	2													
	Controls, 1/10 expt inoc		—	14								2		1			1					
	Controls, 1/100 expt inoc		—	21.5						(1 survivor Day 80)						1			1		1	
	Retransplant recipients		—	10	(from Day 6)										3		1					
	Untreated without tumor		—	—						(6 survivors Day 80)												

[1] BDF_1 male mice, 19–25 g per group; experimental inoc, 7,640,000 cells/mouse; sc treatment begun Day 6.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-500 [1]

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-500 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																		
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]-benzoyl]- (methotrexate)	3.00	14.5		1				2		2	1	2	2									
		1.80	17									1	2	4	1			1	1				
		1.08	21						1							3		2		3		1	
		0.65	14.5			1		3	1					1	(2 survivors Day 26)				1		1		
		0.39	11			1	1	7														1	
	$N_8O_5C_{20}H_{22}$																						
	B																						
56054	Pseudourea, 2,2'-(9,10-anthryl-enedimethylene) bis-[2-thio-, dihydrochloride, dihydrate	80.0†	9†			7	3																
		40.0	9			9	1																
		20.0	9		1	6	3																
		10.0	9			8	1	1															
	$N_4S_2C_{12}H_{18} \cdot 2\ HCl \cdot 2\ HOH$	5.00	9			8	2																
		2.50	9			6	4																
	C	1.25	9			6	3	1															
		0.63	9			7	2	1															
		0.32	9		1	8	1																
		0.16	9			9	1																
60542	Ethane, 1,2-dimethoxy-	1500	12.5			2	1		2	2	2	1											
		1000	13					1	2	5	2												
	$O_2C_4H_{10}$	666	11			4	1		1	2	1			1									
		444	9			8	1	1															
	D	296	9			7	2		1														
		197	9			6	4																
		131	9			8	2																
529064	Urea, 1-hydroxy-1-methyl-	300†	14†					1	1	2	2	2		2									
	$N_2O_2C_2H_6$	180	13				1	2		5	2												
		108	11				3	3	1	1	2												
	D	65.0	10			3	4	3															
		39.0	9		1	5	4																
		23.0	9.5			5	5																
42330	Glucopyranose, 6-[(2-chloro-ethyl) methylamino]-6-deoxy-, hydrochloride, D-	300†	9†			10																	
		180	9			6	2	2															
		108	9		1	7	1	1															
		65.0	9			6	4																
	$NO_5ClC_9H_{12} \cdot HCl$	39.0	9		1	7	2																
		23.0	9.5			5	5																
	C																						
	Controls, expt inoc	—	9.5			5	5																
	Controls, expt inoc	—	10			4	5	1															
	Controls, 1/10 expt inoc	—	13.5					1		1	1	1											
	Controls, 1/100 expt inoc	—												(3 survivors Day 26)						1			
	Retransplant recipients	—	10 (from Day 7)								1			3									
	Untreated without tumor	—	—																			(6 survivors Day 26)	

[1] BDF_1 male mice, 19–25 g per group; experimental inoc, 5,872,000 cells/mouse; daily sc treatment begun Day 7.

†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.

‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-502 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	

| | | |

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-505 [1]

NSC No.	Compound molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	29	32	35	41	42
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (methotrexate)	4.00	16.5								2		1	1	2	1	1												
		2.00	18.5										1	2		1	3	1											
		1.00	24.5						1									1			1	1	3		1				
		0.50	11					3	2									2			1								
		0.25	9				5	2				1																	
	$N_8O_6C_{20}H_{22}$																												
	B																												
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytarabine hydrochloride)	80.0	16									1	1	3	2	1													
		40.0	15									2	3	1			1						1						
		20.0	41.5													(8 survivors Day 42)							1		1	1	1	1	
		10.0	24																1			4	1	2					
		5.00	24.5																1		2	1	1	3					
	$N_3O_3C_9H_{13}$·HCl																												
	A																												
31712	Orotic acid, 5-fluoro-, monohydrate	40.0	15									3	4	1															
		20.0	14								1	7																	
		10.0	13.5							1	3	2	1	1															
	$N_2O_4FC_5H_3$·HOH	5.00	11.5					3	1	2	2																		
		2.50	9			2	3	2	1																				
	C																												
64333	Orotic acid, 5-fluoro-, methyl ester	80.0	13		1	1				1	3	2																	
		40.0	13.5		1	1					2	3	1																
		20.0	14								2	5	1																
	$N_2O_4FC_6H_5$	10.0	13.5				1	1	1		1	2	1	1															
		5.00	9.5		1		3	2	2																				
	C	2.50	8		1	4	1	1				1																	
	Controls, expt inoc	—	8			5	2	1																					
	Controls, expt inoc	—	9			3	4	1																					
	Controls, 1/10 expt inoc	—	11					1	2								1												
	Controls, 1/100 expt inoc	—	19.5										1			1			1						(1 survivor Day 42)				
	Retransplant recipients	—	8.5 (from Day 6)									2	2																
	Untreated without tumor	—	—																						(6 survivors Day 42)				

[1] BDF_1 male mice, 19–27 g per group; experimental inoc, 4,940,000 cells/mouse; daily sc treatment begun Day 6.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-514 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																				
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (methotrexate)	4.00	13						2	4		2												
		2.00	16		1								4		3									
		1.00	20			1		2							1				1		1	1		1
		0.50	19			2			1						1		1	1			1	1		
		0.25	10			2	4	1							1									
	$N_8O_5C_{20}H_{22}$																							
	B																							
56054	Pseudourea, 2,2′-(9,10-anthrylenedimethylene)bis-[2-thio-, dihydrochloride, dihydrate	300†	9†			6	2																	
		180	9		1	4	3																	
		108	9			6	2																	
		65.0	9			8																		
		39.0	9.5			4	1	3																
	$N_4S_2C_{12}H_{18} \cdot 2\ HCl \cdot 2\ HOH$																							
	C																							
529064	Urea, 1-hydroxy-1-methyl-	600	11.5			4					4													
		360	13.5		1	1				2	2	2												
	$N_2O_2C_2H_6$	216	11.5		3	1					2	2												
		130	10		2	2		1		1		1	1											
	D	78.0	12.5			1	1	1	1	1	1	1	1											
42330	Glucopyranose, 6-[(2-chloroethyl)methylamino]-6-deoxy-, hydrochloride, D-	600	8		6	2																		
		360	9			7	1																	
		216	9			5	2	1																
		130	9			5	2	1																
	$NO_5ClC_9H_{18} \cdot HCl$	78.0	9			7	1																	
	C																							
22837	Guanosine, 2′-deoxy-	1000	9		1	7																		
		600	9		1	7																		
	$H_2O_4C_{10}H_{13}$	360	9		1	5	2																	
		216	9			8																		
	A	130	9		2	4	2																	
69856	Neocarzinostatin, crystalline antibiotic (Formula unknown)	500	11			4				2	2													
		250	10.5			3	1	2	1			1												
		125	9		1	4	3																	
		62.5	9		1	5	2																	
	D	31.2	9		2	4	2																	
87206	6*H*-Pyrido[4,3-*b*]-carbazole, 5-methyl-	280	9		1	7																		
		140	9			8																		
		70.0	9		3	5																		
	$N_2C_{16}H_{12}$	35.0	9		3	3	2																	
		17.5	9			6	2																	
	F																							

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-514 [1]—Continued

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																				
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
	Controls, expt inoc	—	9			6	2																	
	Controls, expt inoc	—	9			6	2																	
	Controls, 1/10 expt inoc	—	11.5					2	2															
	Controls, 1/100 expt inoc	—	15									2						1						
	Retransplant recipients	—	11	(from Day 7)								1			3									
	Untreated without tumor	—	—																		(6 survivors Day 27)			

[1] BDF_1 male mice, 19–26 g per group; experimental inoc, 2,616,000 cells/mouse; daily sc treatment begun Day 7.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-520 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																	
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	15.5							2	1	2	2	1	1	1					
		1.80	16					1	1	1		2		1	2	2					
		1.08	18									4	1				2	2	(1 survivor Day 24)		
		0.65	17									2	1	4	(1 survivor Day 24)					1	1
		0.39	12						6		1	1									2
	$N_8O_5C_{20}H_{22}$																				
	B																				
94600	Camptothecin	1.00†	11†			1	1	5	1	2											
		0.60	10			2	4	4													
	$N_2O_4C_{20}H_{16}$	0.36	9		1	5	4														
		0.22	10			3	4	3													
	E	0.13	10		1	1	7	1													
		0.08	9			9	1														
		0.05	10			4	6														
	Controls, expt inoc	—	9		1	5	2	2													
	Controls, expt inoc	—	9			6	3	1													
	Controls, 1/10 expt inoc	—	13						2	2	1	1									
	Controls, 1/100 expt inoc	—	—									1	1						(4 survivors Day 24)		
	Retransplant recipients	—	8	(from Day 7)						1	1	5									
	Untreated without tumor	—	—																(10 survivors Day 24)		

[1] CDBA male mice, 19–26 g per group; experimental inoc, 3,536,000 cells/mouse; daily sc treatment begun Day 7.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-521 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]-benzoyl]- (methotrexate)	3.00	12					2	5	1		1	1							
		1.80	14					2		2	4	2								
		1.08	14.5								5	3			1		1			
		0.65	18						1			2	1		2		3		1	
	$N_8O_5C_{20}H_{22}$	0.39	13					4	1		1		2	2						
	B																			
45388	Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-	833	13.5			1	2			2	5									
		500	10			4	2	1		1	1	1								
		300	9		1	9														
	$N_6OC_6H_{10}$	180	9		1	8	1													
		108	9			10														
	E	65.0	9			9	1													
42076	Podophyllotoxin, 4,6-*O*-benzylidene-β-D-glucoside	833	10.5		3		2	2	3											
		500	9			7	2		1											
		300	9			9		1												
	$O_{12}C_{25}H_{26}$	180	9			9	1													
		108	9			8	2													
	F																			
49928	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α'-(hydroxymethyl)-, monohydrochloride	180	9			10														
		108	10			3	7													
		65.0	12			1	1		8											
		39.0	9			6	2	1	1											
	$N_5O_4C_{10}H_{11}\cdot HCl$	23.0	9.5			5	1	4												
		14.0	9			8	2													
	E																			
74944	8-Quinolinol, 5-fluoro-	500	8		6	4														
		300	9		4	4	2													
	$NOFC_9H_6$	180	9		1	8	1													
		108	9		2	8														
	F	65.0	9			10														
		39.0	9			7	3													
	Controls, expt inoc	—	9		1	9														
	Controls, expt inoc	—	9			10														
	Controls, 1/10 expt inoc	—	11					6												
	Controls, 1/100 expt inoc	—	12						4	1	1									
	Retransplant recipients	—	8	(from Day 7)								6	2							
	Untreated without tumor	—	—												(8 survivors Day 23)					

[1] CDBA male mice, 19–26 g per group; experimental inoc, 8,140,000 cells/mouse; daily sc treatment begun Day 7.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-522 [1]

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-523 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment route	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 7 through 10	11 through 15	16 through 20	21 through 25	26 through 30	31 through 35	36 through 40	41 through 45	46 through 50	51 through 55	56 through 60	61 through 84
					(Mice with leukemia L1210)												
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-(methotrexate)	sc	Daily	3.00	11.5		8										
				1.80	12		7	1									
				1.08	21		8	1	3	1							
				0.65	28.5			2	1	3	2						
				0.39	16.5			5	2	1							
	$N_8O_6C_{20}H_{22}$																
	B																
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside; ara-C)	sc	Daily	65.0	25		1		4	1	2						
				39.0	32.5				1	3		2	1	1			
				23.0	52					2	1	1	(1 survivor Day 84)				8
				14.0	28.5				3	2	1	1			1		
	$N_3O_4C_9H_{13}$·HCl			8.40	27				3	2	1	1	1				
	A	sc	4 times daily	14.0	23.5			2	3	2	1						
				8.40	74					1	2		(3 survivors Day 84)				2
				5.00	44.5	(1 survivor Day 84)			1	1	1	1		1			2
				3.00	29					5				1		2	
				1.80	28				3	2				1			2
		sc	Twice daily	39.0	36.5					3	1	1	1	1	1		
				23.0	>74					1		1	(4 survivors Day 84)			1	1
				14.0	62.5				1		1			1		1	4
				8.40	44		1			2		1			3	1	
				5.00	28		2		1	3		2					
		Oral	Daily	108	27				1	5	2						
				65.0	25.5				4	1	1				1	1	
				39.0	26.5				3	5							
				23.0	26		1		2	4	1						
				14.0	22		3		2	2							
		Oral	4 times daily	30.0	16		4	3		1							
				23.0	17.5		2	3		1	1			1			
				14.0	34			1	1	2		1	2	1			
				8.40	30					5		2					1
				5.00	32.5			1		3	1	2					1
		Oral	Twice daily	65.0	32				1	1	3	1	1				1
				30.0	26.5			1	2	2	1			1			1
				23.0	25		1		3	4							
				14.0	13	2	3		2	1							
				8.40	11	3	3		1	1							
		Oral	Every 2 days	833	13.5		8										
				500	16		3	4	1								
				300	29	1		1	1	2	2		1				
				180	26			1	1	4	1						1

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-523 [1]—Continued

NSC No.	Compound, molecular formula, and vehicle[‡]	Treatment route	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 7 through 10	11 through 15	16 through 20	21 through 25	26 through 30	31 through 35	36 through 40	41 through 45	46 through 50	51 through 55	56 through 60	61 through 84
				108	25		1	1	2	2	1						1
				65.0	22.5		2	2		2	1						1
	Controls, expt inoc			—	9.5	7	1										
	Controls, expt inoc			—	10	8											
	Controls, 1/10 expt inoc			—	11	1	2	1									
	Controls, 1/100 expt inoc			—	13		4										
	Retransplant recipients			—	9	(from Day 7)	2	6									
	Untreated without tumor																
					(Mice without tumors)												
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside; ara-C)	sc	Daily	65.0	24		1	2	1	4							
				39.0	26				3	2	1			1			1
				23.0										(8 survivors Day 84)			
				14.0										(8 survivors Day 84)			
	$N_3O_6C_9H_{13} \cdot HCl$			8.40										(8 survivors Day 84)			
	A																
		sc	4 times daily	14.0	16		4	3	1								
				8.40						3							
				5.00										(7 survivors Day 84)			1
				3.00									(7 survivors Day 84)	1			
				1.80									(8 survivors Day 84)				
		sc	Twice daily	39.0	26			1	3	2			1			1	
				23.0										(8 survivors Day 84)			
				14.0				1						(7 survivors Day 84)			
				8.40							(7 survivors Day 84)	1					
				5.00							(8 survivors Day 84)						
		sc	Every 2 days	500	34.5				3		1	1	1	(2 survivors Day 84)			
				300				1		1	1		(4 survivors Day 84)	1			
				180	23			1	4					(3 survivors Day 84)			
				108										(7 survivors Day 84)			
				65.0				1						(7 survivors Day 84)			
				39.0										(7 survivors Day 84)			
		Oral	Daily	108	23.5			1	2	2	1			(2 survivors Day 84)			
				65.0			1				(6 survivors Day 84)	1					
				39.0					1		(6 survivors Day 84)	1					
				23.0							(7 survivors Day 84)	1					
				14.0							(7 survivors Day 84)						1
		Oral	4 times daily	39.0	15		6	2									
				23.0	16.5		3	3		1				(1 survivor Day 84)			
				14.0	19		2	3						(3 survivors Day 84)			
				8.40			1	2		1				(4 survivors Day 84)			
				5.00					1		1			(4 survivors Day 84)			
		Oral	Twice daily	65.0				1					1	1	(5 survivors Day 84)		
				39.0											(8 survivors Day 84)		

	Oral	Twice daily	65.0			1					1	1	(5 survivors Day 84)
			39.0										(8 survivors Day 84)
			23.0				(6 survivors Day 84)				1		1
			14.0			1							(7 survivors Day 84)
			8.40										(8 survivors Day 84)
	Oral	Every 2 days	833	17.5	2	4		1	1				
			500	21.5	1	3	1	1	1	1			
			300	48	1		1					6	
			180		(5 survivors Day 84)			1				1	1
			108		1								(7 survivors Day 84)
			65.0		1		2						(5 survivors Day 84)

[1] CDBA male mice, 19–27 g per group; experimental inoc, 7,080,000 cells/mouse; treatment begun Day 7.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-524 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
740	Glutamic acid, *N*-[*p*-	3.00	17									2		1	3			2							
	[[(2,4-diamino-6-pteridinyl)-	1.80	22				(1 survivor Day 27)					1		1				1		2		1			1
	methyl]methylamino]-	1.08	27															(3 survivors Day 27)			1	1		1	2
	benzoyl]- (methotrexate)	0.65	26					2										(1 survivor Day 27)					1	3	1
		0.39	14					1	2			3									1			1	
	$N_8O_6C_{20}H_{22}$																								
	B																								
87206	6*H*-Pyrido[4,3-b]carbazole, 5-	20.0	9				5	1																	
	methyl-	15.0	9.5				3	3																	
		10.0	9				5	1																	
	$N_2C_{16}H_{12}$																								
	F																								
	Controls, expt inoc	—	9				5	3																	
	Controls, expt inoc	—	10				2	6																	
	Controls, 1/10 expt inoc	—	11.5						2	1		1													
	Controls, 1/100 expt inoc	—	15.5									1	1	1				1							
	Retransplant recipients	—	10	(from Day 6)									1	4	1										
	Untreated without tumor	—	—																	(6 survivors Day 27)					

[1] BDF_1 male mice, 20–27 g per group; experimental inoc, 3,740,000 cells/ mouse; daily sc treatment begun Day 6,
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-526 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	33	40
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methyl-amino]benzoyl]-(methotrexate)	3.00	19									2		1	2		1	4												
		1.80	24										1	1				1	1		2	1	2		1					
		1.08	24												1				1	2	2	2		2					
		0.65	28						2														1	1	2		2	2		
		0.39	16.5					1	3		1					1											2	2	
	$N_8O_5C_{20}H_{22}$																													
	B																													
94600	Camptothecin	3.00	13						1	6	2	1																		
		1.80	13.5						2	3	1	3	1																	
	$N_2O_4C_{20}H_{16}$	1.08	11					7	3																					
		0.65	11				1	7	1	1																				
	G																													
49271	2(1*H*)-Pyridone, 1,5-dihydroxy-6-methyl-	500†	11†			1		7	2																					
		300	11					8	2																					
		180	11					8		2																				
		108	11				2	8																						
	$NO_3C_6H_7$	65.0	11				3	4	2	1																				
	E																													
51915	Cyclohexanecarboxamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis-	1388†	11†				1	9																						
		833	11					9	1																					
		500	11					7	2	1																				
		300	11					9		1																				
		180	11					8	2																					
	$N_6O_4C_{24}H_{22}$																													
	E																													
18269	Acetamide, *N,N'*-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]-bis-	8.40	12						3	2																				
		5.00	13						3	6		1																		
		3.00	15						1	2	1	3	3																	
		1.80	18								1		2	1	2	4														
		1.08	23.5									1						1	1	2	1	2	2							
		0.65	14.5							1	4	2				1					1	1								
	$N_4O_4C_{14}H_{16}$																													
	D																													
	Controls, expt inoc	—	11					10																						
	Controls, expt inoc	—	11				1	9																						
	Controls, 1/10 expt inoc	—	13					1		1		1																		
	Controls, 1/100 expt inoc	—									1								1						(2 survivors Day 40)				

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-526 [1]—Continued

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																									
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	33	40
	Retransplant recipients	—	10.5 (from Day 7)										1	3	2	2													
	Untreated without tumor	—	—																										(6 survivors Day 40)

[1] BDF_1 male mice, 19–26 g per group; experimental inoc, 4,900,000 cells/mouse; daily sc treatment begun Day 7.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-530 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	26	29	31	32
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	Daily from Day 3	1.80	13.5									1	2	1	1	1			1	1									
			1.08	27.5																		1	1			1	1	1	2	1
			0.65	23																		1		2	2		1	1	1	
			0.39	12								2	1	2		3														
			0.23	12										6	1	1														
	$N_8O_5C_{20}H_{22}$																													
		Daily from Day 6	3.00	12.5									2	2	1	2				1										
	B		1.80	16										1	1	1		2	1	2										
			1.08	15.5									2		1		1	1		2										
			0.65	14									2	1	1		2									2				
			0.39	9.5							4	2	1			1														
45388	Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-	Daily from Day 3	833	10							3	4	1																	
			500	14.5										2	1	1	2	2												
			300	17													1	2	2	2	1									
	$N_5OC_5H_{10}$		180	15											1	3		1	1		2									
			108	13								1	1		4	2														
	E																													
		Daily from Day 6	1388	14										2		5	1													
			833	9						3	5																			
			500	9						1	7																			
			300	9						1	6	1																		
			180	9							6	2																		
94100	Mannitol, 1,6-dibromo-1,6-dideoxy-, D-	Daily from Day 3	500	9							5	2			1															
			300	9						1	6	1																		
			180	9							7	1																		
	$O_4Br_2C_6H_{12}$		108	9							8																			
			65.0	9						2	6																			
	E																													
		Daily from Day 6	500	9						1	7																			
			300	9						1	7																			
			180	8.5						4	4																			
			108	9						1	7																			
			65.0	9						3	5																			
	Controls, expt inoc		—	9						2	5			1																
	Controls, expt inoc		—	9							8																			
	Controls, 1/10 expt inoc		—	10							1	3	1		1															
	Controls, 1/100 expt inoc		—	12.5										3	3															
	Retransplant recipients		—	8 (from Day 6)										1	2	3	2													
	Untreated without tumor		—	—																		(10 survivors Day 32)								

[1] CDBA male mice, 18–24 g per group; experimental inoc, 4,900,000 cells/mouse; daily sc treatment begun Day 3 or Day 6.

‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-533 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	35
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]-benzoyl]- (methotrexate)	3.00	18.5						1			1	1	1	2		1		1								
		1.80	24.5															1	2	1	2		1		1			
		1.08	27																1	1	2				1	1	2	
		0.65	25.5				1	1				1								1			1	1			2	
		0.39	20.5				1	1		2													1		1	2		
	$N_8O_5C_{20}H_{22}$																											
	B																											
77556	9*H*-Purine-6-thiol, 2-amino-9-*β*-D-ribofuranosyl-, 2′,3′,5′-tripropionate	39.0†	14.5†	1	2		1						2	2														
		23.0	11		2	3	2	1																				
		14.0	12		1	2	3	1	1																			
		8.40	14.5			4								1		2	1											
	$N_8O_7SC_{29}H_{35}$	5.00	11		1	4	1					1	1															
	E																											
13002	Acridine, 9-[*p*-dimethylamino)anilino]-	720†	15.5†					2	2					2	1	1												
		432	12.5				3	1	2					1			1											
		259	12				2	4	1		1																	
	$N_3C_{21}H_{19}$	155	12.5					4	4																			
		98.0	11.5		1	3	3									1												
	D																											
	Controls, expt inoc	—	11		2	3		1	1	1																		
	Controls, expt inoc	—	11		1	4	1	2																				
	Controls, 1/10 expt inoc	—	18.5							1	1			1	1		(2 survivors Day 35)											
	Controls, 1/100 expt inoc	—	—									1					(5 survivors Day 35)											
	Retransplant recipients	—	9 (from Day 8)									3	5															
	Untreated without tumor	—	—														(8 survivors Day 35)											

[1] BDF_1 male mice, 19–28 g per group; experimental inoc, 5,600,000 cells/mouse; daily sc treatment begun Day 8.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-536 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	31
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	16							1	1	5		1												
		1.80	17.5										4	2	1				1							
		1.08	24				1						1					1		2			2	1		
		0.65	27.5			1	1																2	2	1	1
		0.39	12			1	1	3	2	1																
	$N_8O_5C_{20}H_{22}$																									
	B																									
18270	*p*-Benzoquinone, 2,5-bis(1-aziridinyl)-3,6-diethoxy-	23.0	12			1	2	5																		
		14.0	13.5					1	3	4																
		8.40	14				1	1	1	4	1															
	$N_2O_4C_{14}H_{18}$	5.00	15			1		2			5															
		3.00	12			1	2	2	2	1																
	E																									
83693	Butyric acid, 4-[*p*-(3,3-dimethyl-1-triazeno)phenyl]-, hydrazide	180	12.5				1	3	1	3																
		108	12			3	1		1	3																
		65.0	12			2	2		2		2															
	$N_5OC_{12}H_{19}$	39.0	13				1	1	4	1	1															
		23.0	12					7		1																
	E																									
87982	Imidazole-4-carboxylic acid, 5-(3,3-dimethyl-1-triazeno)-, methyl ester	108†	17.5†							1	1		2	3	1											
		65.0	11.5			4			1		1			1	1											
		39.0	12			1	2	4					1													
		23.0	11			3	4		1																	
	$N_5O_2C_7H_{11}$	14.0	12			1	1	5								1										
	D																									
1895	Guanazole	2000†	16.5†							2		3	1	2	1											
		1200	14						1	5				1	1											
	$N_5C_2H_5$	720	12				2	3	2	1																
		432	11.5			1	3	4																		
	Controls, expt inoc	—	11			1	4	2		1																
	Controls, expt inoc	—	11			1	6	1																		
	Controls, 1/10 expt inoc	—	15.5							2	1	1		1			1									
	Controls, 1/100 expt inoc	—	23.5								1					1				(2 survivors Day 31)						
	Retransplant recipients	—	9 (from Day 8)									2	5	1												
	Untreated without tumor	—	—																	(3 survivors Day 31)						

[1] BDF_1 male mice, 19–26 g per group; experimental inoc, 4,656,000 cells/mouse; daily sc treatment begun Day 8.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-541 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																			
				7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	12					3	3	1			1									
		1.80	14.5						2		2	2	1	1								
		1.08	22				(2 survivors Day 25)							1	1	1			2		1	
		0.65	22				(2 survivors Day 25)											3	3			
		0.39	15					1	3						1	3						
	$N_8O_6C_{20}H_{22}$																					
	B																					
18270	*p*-Benzoquinone, 2,5-bis(1-aziridinyl)-3,6-diethoxy-	23.0	11				3	2	3													
		14.0	12				2		5	1												
		8.40	12.5					2	2	3		1										
	$N_2O_4C_{14}H_{18}$	5.00	13			1			2	2	1	2										
		3.00	12.5				1	2	1	2		2										
	E																					
1895	Guanazole	2000	14							3	2	2	1									
		1200	13.5			1		1		2	2		1	1								
	$N_8C_2H_8$	720	13				1	2		3	1		1									
		432	12.5				1	1	2	2	1	1										
	A	259	11				2	3	3													
403144	Colchiceinamide	16.0	12					2	4	1	1											
		8.00	12				3		3			2										
	$N_2O_6C_{21}H_{26}$	4.00	12				2		3	3												
		2.00	12				2	1	2	1		1	1									
	A	1.00	10			1	4	1	1	1												
50164	Colchicine, demethyl-	20.0	10			1	5	1	1													
		15.0	12			2	1		2	1		2										
	$NO_6C_{21}H_{23}$	7.50	12					2	3	1	1			1								
		3.80	11			1	2	2		1			1		1							
	E	1.80	10			3	2	2			1											
	Controls, expt inoc	—	11.5				1	3	2	2												
	Controls, expt inoc	—	11				3	3		1		1										
	Controls, 1/10 expt inoc	—	12					2	2			1	1									
	Controls, 1/100 expt inoc	—	15							1		4				(1 survivor Day 25)						
	Untreated without tumor	—	—													(10 survivors Day 25)						

[1] CDBA male mice, 19–26 g per group; experimental inoc, 3,712,000 cells/mouse; daily sc treatment begun Day 7.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL–544 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment route	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 5 through 10	11 through 15	16 through 20	21 through 25	26 through 30	31 through 35	36 through 40	41 through 45	46 through 50	51 through 54
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	sc	3.00	21.5		1	2	3	2					
			1.80	26			1	3	4					
			1.08	29				1	5	2				
			0.65	26.5			1		7					
			0.39	12.5		6	1	1						
	$N_8O_5C_{20}H_{22}$													
	B													
63878	Cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride (cytosine arabinoside; ara-C)	sc	80.0	14		7	1							
			40.0	23			2	4		1		1		
			20.0	52		(1 survivor Day 54)			1	1			1	4
	$N_3O_5C_9H_{13}$·HCl		10.0	26.5				3	4	1				
			5.00	26			1		7					
	A													
		Oral	320	14.5		6	1		1					
			160	31.5				1	3	1	2			1
			80.0	28.5				2	5	1				
			40.0	26.5				3	4	1				
			20.0	23				8						
93150	Cytosine, 1-β-D-arabinofuranosyl-, 2′,3′,5′-triacetate	sc	320	13.5		8								
			160	22.5			3	5						
			80.0	36					2	2	2	1	1	
	$N_3O_8C_{12}H_{19}$		40.0	36				1	2	1	2	1	1	
			20.0	29				1	5	1	1			
	E													
		Oral	640	14		5		1	2					
			320	32				2	1	3	2			
			160	26				2	5		1			
			80.0	27			1	2	5					
			40.0	25.5				4	3	1				
			20.0	22	1	1		6						
	Controls, expt inoc		—	10	6	2								
	Controls, expt inoc		—	10	8									
	Controls, 1/10 expt inoc		—	14.5		5	1							
	Controls, 1/100 expt inoc		—	18.5			5			(1 survivor Day 54)				
	Retransplant recipients		—	13	(from Day 5)		8							
	Untreated without tumors		—	—						(8 survivors Day 54)				

[1] BDF_1 male mice, 19–29 g per group; experimental inoc, 4,776,000 cells/mouse; daily treatment begun Day 5.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-545 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																		
				6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	16.5								1		2	1	1	2	1	1				
		1.80	20											1		2		3	2	1		1	
		1.08	19							3	(1 survivor Day 25)					1	2	1		1		1	
		0.65	14.5			2		1	1	1					1				1		2		1
		0.39	9			3	3	3			1												
	$N_6O_5C_{20}H_{22}$																						
	B																						
76955	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2',3',5'-tributyrate	180	12						2	4	4												
		108	13.5							5	5												
		65.0	14							2	2	4	2										
	$N_8O_7SC_{22}H_{31}$	39.0	9			3	3						1	3									
		23.0	8			6	2							2									
	E	14.0	9			4	5	1															
70806	1,3-Propanediamine, *N,N'*-bis(2-chloroethyl)-, dihydrochloride	130	10			1	1	4	4														
		77.8	12.5			1		1	2	1	3	2											
		46.7	13.5			2	1				2	1	3	1									
		28.0	12			3	1			3	2	1											
	$N_2Cl_2C_7H_{16}·2$ HCl	16.8	9			4	5	1															
		10.0	9			2	5	3															
	D																						
83290	2,3-Butanediol, 1,4-bis[(2-chloroethyl)amino]-, dihydrochloride, DL-	108	12					2	2	5	1												
		65.0	11.5			1		1	3	3	2												
		39.0	13						3	2		2	2	1									
		23.0	15			1					1	1	3	4									
	$N_2O_2Cl_2C_8H_{16}·2$ HCl	14.0	13.5			1				2	2	3		2									
	D																						
	Controls, expt inoc	—	8			8	2																
	Controls, expt inoc	—	8			8	2																
	Controls, 1/10 expt inoc	—	14							1	2		1		1	1							
	Controls, 1/100 expt inoc	—	18.5									1		1	1			1 (2 survivors Day 25)					
	Retransplant recipients	—	8	(from Day 6)							3	3	2										
	Untreated without tumor	—	—															(10 survivors Day 25)					

[1] BDF_1 male mice, 21–30 g per group; experimental inoc, 3,320,000 cells/mouse; daily ac treatment begun Day 6.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-550 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	13								2	5		1																
		1.80	15.5								1	2		1	2	1	1													
		1.08	21												1			2		2		1				1	1			
		0.65	24.5				1											2				1			1	1		1	1	
		0.39	15.5				1	2	1											1	1						2			
	$N_8O_6C_{20}H_{22}$																														
	B																														
70631	Glutamic acid, *N*-[bis(2-chloroethyl)carbamoyl]-, diethyl ester, L-	500†	9†				3	5																						
		300	8			2	4	2																						
		180	8				6	2																						
		108	9				3	3	2																					
	$N_2O_5Cl_2C_{14}H_{24}$	65.0	8.5				4	4																						
	A																														
91741	Urea, 1-(2-chloroethyl)-1-nitroso-3-(2,6-xylyl)-	108	13							1	2	2	2	1								1	2			2	1		1		1
		65.0	27																												
		39.0	23										1				1	1				3			1		1				
	$N_3O_2ClC_{11}H_{14}$	23.0	14.5							1		1	2	1			1	2													
		14.0	10					2	4	1	1																				
	C	8.40	8.5				4	3						1																	
65005	Adenine, 9-[2-[bis(2-chloroethyl)-amino]ethyl]-, dihydrochloride, monohydrate	39.0	10					2	6																						
		23.0	10.5						4	3	1																				
		14.0	11						3	3	2																				
		8.40	9				1	5	2																						
	$N_6Cl_2C_{11}H_{16} \cdot 2\ HCl \cdot HOH$	5.00	9				2	5	1																						
	C																														
37917	Streptozotocin	500	8			1	7																								
		300	9				2	6																							
	$N_3O_{12}C_{14}H_{27}$	180	9				2	6																							
		108	8				5	3																							
	D	65.0	9				2	6																							
		39.0	8			1	4	3																							
	Controls, expt inoc	—	8				5	3																							
	Controls, expt inoc	—	8.5				4	4																							
	Controls, 1/10 expt inoc	—	10.5						2	1				1																	
	Controls, 1/100 expt inoc	—	13									3				1															
	Retransplant recipients	—	8.5 (from Day 5)									4	3	1																	
	Untreated without tumor	—	—																			(6 survivors Day 32)									

[1] BDF_1 male mice, 19–25 g per group; experimental inoc, 4,700,000 cells/mouse; daily sc treatment begun Day 5.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-555[1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]-benzoyl]- (methotrexate)	3.00	17							2				2				3							
		1.50	23											1	1	(2 survivors Day 26)					1	2	1		
		0.75	22													1				3		2	2		
		0.37	11					2		3		1	1							1					
	$N_5O_5C_{20}H_{22}$																								
	B																								
70806	1,3-Propanediamine, *N,N'*-bis(2-chloroethyl)-, dihydrochloride	80.0	13.5							1		3	2		2										
		40.0	9				2	4	2																
		20.0	9				2	6																	
	$N_2Cl_2C_7H_{16}$·2 HCl	10.0	9				3	5																	
		5.00	8.5				4	4																	
	D																								
42343	Propionic acid, 3(o-[bis(2-chloroethyl)amino]phenoxy)-	30.0†	8†				7	1																	
		15.0	8				5	3																	
		7.50	8				5	3																	
	$NO_2Cl_2C_{13}H_{17}$	3.75	8				5	3																	
	E																								
70088	Purine-6-thiol, disodium salt, compd. with bismuth oxide (Bi O) (3:1), trihydrate	60.0†	13†				2				1	3	2												
		30.0	9					3																	
		15.0	8				5	2	1																
		7.50	9				1	4	3																
	$N_3SC_5H_4$·Na salt·$\frac{1}{3}$ (Bi O)·3 HOH																								
	E																								
81159	*meso*-2,3-Butanediol, 1,4-bis[(meso-2-chloro-1-methylethyl)[or(*meso*-2-chloropropyl)]amino]-, dihydrochloride (isomer B)	30.0	10					3	4	1															
		15.0	12							3	2	2	1												
		7.50	13							1	2	5													
		3.75	9				1	4	3																
		1.87	9				2	3	3																
	$N_2O_2Cl_2C_{10}H_{22}$·2 HCl																								
	D																								
	Controls, expt inoc	—	8.5				4	4																	
	Controls, expt inoc	—	9				5	5																	
	Controls, 1/10 expt inoc	—	11.5						1	1	2														
	Controls, 1/100 expt inoc	—	12.5								2	2													
	Retransplant recipients	—	10 (from Day 5)										2	6											
	Untreated without tumor	—	—															(6 survivors Day 26)							

[1] BDF_1 male mice, 19–28 g per group; experimental inoc, 4,620,000 cells/mouse; daily sc treatment begun Day 5.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 28.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

‡See footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-556 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	29	30	31	32	33	34	35	36	37	38	41	42
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]benzoyl]-(methotrexate)	3.00	18				*					1		1			2	1	1	1																
		1.50	20															1	4	1	2																
		0.75	20.5														1	1	2	2	1	1															
		0.37	21															1		4			3														
	$N_8O_5C_{20}H_{22}$																																				
	B																																				
77517	Urea, [α-(2-methylhydrazino)-*p*-toluoyl]-, monohydrobromide	400	8			1	4	2		1																											
		200	9				3	4	1																												
		100	9				3	4		1																											
		50.0	8				5	2		1																											
	$N_4O_2C_{10}H_{14} \cdot HBr$																																				
	D																																				
88106	Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso-	60.0	17											2	1	2	1	1	1																		
		30.0	24.5									1			1			1					1	1	1										1	1	
		15.0	10					3	2									1		1								(1 survivor Day 42)								
		7.50	8				5	1	1	1																											
	$N_3O_2ClC_{10}H_{16}$	3.75	8				7	1																													
	E																																				
87974	Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso-	30.0	18									1	1	1		1		2	1	1						1	1				2	2	1			
		15.0	33.5																																		
		7.50	32					1																1		1	1						1				
		3.75	9.5				1	3	3		1																										
	$N_3O_2FC_9H_{16}$	1.85	8.5				4	4																													
	E																																				
65005	Adenine, 9-[2-[bis-(2-chloroethyl)-amino]ethyl]-, dihydrochloride, monohydrate	30.0	9			1		4	3																												
		15.0	10					2	4	2																											
		7.50	9				1	7																													
		3.75	8				5	3																													
		1.85	8.5				4	4																													
	$N_5Cl_2C_{11}H_{19} \cdot 2\ HCl \cdot HOH$																																				
	D																																				

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-556[1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																																
				5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	29	30	31	32	33	34	35	36	37	38	41	42
69185	*p*-Cymene-2-sulfonic acid, 5-hydroxy-, compd. with 1,1′-[(methylethanediylidene)dinitrilo]diguanidine (2:1)	250	12.5								4	1		1		1	1																			
		125	11						3	2	2		1																								
		62.5	9				2	5			1																									
		31.2	8				7	1																												
	$O_4SC_{10}H_{14} \cdot \frac{1}{2} N_8 C_8H_{12}$																																			
	E																																			
82196	Imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]-	400	15									1		4	2	1																				
		200	18.5													1	3	3	1																	
		100	23.5																	1	1	2	1				1		1			1				
		50.0	30.5																			2		1				1	1		1	1				1
		25.0	14.5							1			3	2			2																			
	$N_8OCl_2C_8H_{12}$																																			
	E																																			
	Controls, expt inoc	—	8				5	3																												
	Controls, expt inoc	—	9				3	5																												
	Controls, 1/10 expt inoc	—	9.5					2	2																												
	Controls, 1/100 expt inoc	—	12							2		1	1																								
	Retransplant recipients	—	9	(from Day 5)							1	1	6																								
	Untreated without tumor	—	—																													(6 survivors Day 42)				

[1] CDBA male mice, 19–27 g per group; experimental inoc, 6,820,000 cells/mouse; daily ss treatment begun Day 5.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-564 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 39 40 43 47 48 52 55
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (methotrexate)	3.00	15	1 2 3 1 1 1 2 2 2 1
		1.50	22	2 1 2 1
		0.75 •	23	2 1
		0.37	12	1 2 1 1 1 1 1
	$N_8O_6C_{20}H_{22}$	0.19	9	1 7
	B			
76954	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-, 2′,3′,5′-tris(*p*-chlorobenzoate)	200†	12†	2 2 2 2
		100	9	3 3 2
		50.0	8	5 3
		25.0	8.5	4 3 1
	$N_8O_7SCl_3C_{31}H_{22}$	12.5	8	5 3
	E			
88104	Urea, 3-2-chlorocyclohexyl)-1-(2-chloroethyl)-1-nitroso-, *trans*-	180	10	3 5
		90.0	12	1 1 5 1
		45.0	24	1 1 1 2 1 1 1
	$N_3O_2Cl_2C_9H_{15}$	22.5	39.5	1 1 2 2
		11.3•	>53.5•	(4 survivors Day 55) 2 1 1
	E			
42343	Propionic acid, 3-[*o*-[bis(2-chloroethyl)amino]phenoxy]-	150†	9†	3 4 1
		75.0	8	5 3
		37.5	8	1 6 1
	$NO_3Cl_2C_{13}H_{17}$	18.7	8	5 3
	E			
70088	Purine-6-thiol, disodium salt, compd. with bismuth oxide (Bi O) (3:1), trihydrate	200	14	1 2 4 1
		100	15	2 1 4 1
		50.0	9	6 2
		25.0	9	2 5 1
	$N_4SC_5H_4 \cdot Na$ salt $\cdot \frac{1}{2}$ (Bi O) $\cdot$ 3 HOH			
	E			
	Controls, expt inoc	—	8.5	4 4
	Controls, expt inoc	—	8	5 3
	Controls, 1/10 expt inoc	—	9.5	2 2
	Controls, 1/100 expt inoc	—	15	1 1 2
	Retransplant recipients	—	9.5	4 3 1
	Untreated without tumor		—	(8 survivors Day 55)

[1] BDF_1 male mice, 19–28 g per group; experimental inoc, 5,820,000 cells/mouse; daily sc treatment begun Day 5.

‡ *See* footnote (‡) on page 23.

† No clear evidence of toxicity appeared at any dose level, therefore the optimal dose may be higher than any tested.

• Dose level was toxic as evidenced by body weight loss, therefore the optimal dose may be lower than that tested.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-568[1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment route	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 6–10	11–15	16–20	21–25	26–30	31 through 35	36–40	41–45	46–50	51–55	56–60	61–67
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]-benzoyl]- (methotrexate)	sc	3.00	17		2	5	1								
			1.80	21			4	4								
			1.08	23			2	5	1							
			0.65	24			2	2	4							
	$N_8O_6C_{20}H_{22}$		0.39	15	2	2	1	3								
	B															
409962	Urea, 1,3-bis(2-chloroethyl)-1-nitroso-(BCNU)	sc	8.40	28				3	2	2	1					
			5.00	35				1	2	1	3	1				
			3.00	27				2	3	2			1			
	$N_3O_2Cl_2C_5H_9$															
	D															
79037	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-(CCNU)	sc	23.0	26			1	2	5							
			14.0	38						3	2	2	1			
			8.40†	40†					3	1			2	1	1	
	$N_3O_2ClC_9H_{16}$															
	E															
88106	Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso-	sc	65.0	27.5					3							
			39.0	47.5					1		1	2	1	1	1	1
			23.0	30.5	1				3	2				(2 survivors Day 67)		
	$N_3O_2ClC_{10}H_{16}$															
	E															
87974	Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso-	sc	23.0	29				1	3	4						
			14.0	33		2			1	2	1		1	(1 survivor Day 67)		
			8.40	27.5	2			2	1		1		1	1		
	$N_3O_2FC_9H_{16}$															
	E															
88104	Urea, 3-2-chlorocyclohexyl)-1-(2-chloroethyl)-1-nitroso-, *trans*-	sc	108	13.5		6	2									
			65.0	18.5		1	7									
			39.0	26.5			1	1	5	1						
	$N_3O_2Cl_2C_9H_{15}$		23.0	32					3	4		1				
			14.0†	32†			1		3	1		1			2	
	E															
409962	Urea, 1,3-bis(2-chloroethyl)-1-nitroso-(BCNU)	oral	23.0	15		7	1									
			14.0	18.5		2	5	1								
			8.40	27		1		2	2		2	1				
	$N_3O_2Cl_2C_5H_9$		5.00	49.5					2				2	3	1	
			3.00	19.5	1	3		1	2				1			
	D															
79037	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (CCNU)	oral	39.0	15		4	4									
			23.0	20.5			4	4								

79037	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (CCNU)	oral	39.0	15			4	4							
			23.0	20.5				4	4						
			14.0	39					1			4		1	1	1
	$N_3O_2ClC_9H_{16}$		8.40	42.5	(1 survivor Day 67)				2	1		1		1		2
			5.00	21	1		2		5							
	E															
88106	Urea, 1-(2-chloroethyl)-3-(2-norbornyl)-1-nitroso-	oral	180	13.5			3									
			108	17			1	7								
			65.0	22.5				1	6			1				
	$N_3O_2ClC_{10}H_{16}$		39.0	51.5	(3 survivors Day 67)						2	1		1	1	
			23.0	29	(1 survivor Day 67)				1	3	1	1			1	
	E															
87974	Urea, 3-cyclohexyl-1-(2-fluoroethyl)-1-nitroso-	oral	108	11.5	2		6									
			65.0	15.5			4	4								
			39.0	23			1		7							
	$N_3O_2FC_9H_{16}$		23.0	30.5				1	2	1	1		2	1		
			14.0	>67	1					1						(6 survivors Day 67)
	E															
88104	Urea, 3-2-chlorocyclohexyl)-1-(2-chloroethyl)-1-nitroso-, *trans*-	oral	300	10	5		3									
			180	11			8									
			108	13			8									
	$N_3O_2Cl_2C_9H_{15}$		65.0	15.5			4	4								
			39.0	18			1	4	1		2					
	E		23.0†	31†			1	1		2	3	1				
	Controls, expt inoc		—	10	8											
	Controls, expt inoc		—	9	8											
	Controls, 1/10 expt inoc		—	12.5			6									
	Controls, 1/100 expt inoc		—	15.5			3	2	1							
	Retransplant recipients		—	9	(from Day 6)		7	1								
	Untreated without tumor															(8 survivors Day 67)

[1] BDF_1 male mice, 19–29 g per group; experimental inoc, 7,800,000 cells/mouse; daily treatment begun Day 6.
†Dose level was toxic as evidenced by body weight loss, therefore the optimal dose may be lower than that tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-584 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																										
				6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	41	42	47
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	3.00	13							3	2	1	1		1																
		1.80	15									1	3	2	1																
		1.08	20.5										1	1		1		1	2				1	1							
		0.65	25.5																	2			2	1	1	1	1				
		0.39	11				2	2		2													2								
	$N_5O_5C_{20}H_{22}$																														
	B																														
80362	2,5-Pyridinedicarboxanilide, 4′,4″-bis(1,4,5,6-tetrahydro-2-pyrimidinyl)-, dihydrochloride, dihydrate	23.0	9		2		4	1														1									
		14.0	8		2	2	3																								
		8.40	9			2	6																								
		5.00	9			2	6																								
		3.00	9			3	5																								
	$N_7O_2C_{27}H_{27} \cdot 2\ HCl \cdot 2\ HOH$																														
	A																														
18274	Butyramide, *N*,*N*′-[3,6-bis(1-aziridinyl)-*p*-benzoquinon-2,5-ylene]bis-	23.0	11						7	1																					
		14.0	13.5							1	3	4																			
		8.40	16.5										3	1	1	2	1														
		5.00	13			1				1	6																				
	$N_4O_4C_{18}H_{24}$	3.00	10				1	4	2																						
		1.80	9				8																								
	D																														
44426	Acetic acid, [*p*-[bis(2-chloroethyl)-amino]phenoxy]-, ethyl ester	20.0	9			1	7																								
		15.0	8.5			4	4																								
		10.0	9			1	7																								
	$NO_3Cl_2C_{14}H_{19}$	5.00	9			1	7																								
	E																														
93161	Urea, 3-(1-adamantyl)-1-(2-fluoroethyl)-1-nitroso-	108	18				2						1			5															
		65.0	35				3											(2 survivors Day 47)								1			1	1
		39.0	12.5			1	3							1		1		(1 survivor Day 47)										1		
	$N_3O_2FC_{12}H_{20}$	23.0	9				8																								
		14.0	9				8																								
	E																														
89207	Urea, 3-(*p*-acetylphenyl)-1-(2-chloroethyl)-1-nitroso-	65.0	19											3		1		1		1		3									
		39.0	16.5							2			1	1	1			2		1											
		23.0	13							4		1	2			1															
	$N_3O_3ClC_{11}H_{12}$	14.0	12.5					2	2			1		1		2															
		8.40	11.5				1	2	1	1	1		1	1																	
	E																														
	Controls, expt inoc	—	9			2	6																								
	Controls, expt inoc	—	9			1	7																								

Controls, expt inoc	—	9			2	6								
Controls, expt inoc	—	9			1	7								
Controls, 1/10 expt inoc	—	10					4	2						
Controls, 1/100 expt inoc	—	12.5							3	3				
Retransplant recipients	—	8	(from Day 6)							1	7			
Untreated without tumor	—	—											(10 survivors Day 47)	

[1] BDF_1 male mice, 22–30 g per group; experimental inoc, 6,880,000 cells/mouse; daily sc treatment begun Day 6.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-585 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation [tumored mice] or treatment initiation [nontumored mice]) 6–10	11–15	16–20	21–25	26–30	31–35	36 through 40	41–45	46–50	51–55	56–60	61–75
					(Mice with leukemia L1210)											
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]- (methotrexate)	Daily	3.00	23.5			3	3	1		1					
			1.80	29	1		1		3	3						
			1.08	29.5	1				4	3						
			0.65	20.5	1	3			3	1						
			0.39	11	3	4	1									
	$N_8O_5C_{20}H_{22}$															
	B															
409962	Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (BCNU)	Single injection	65.0	13.5		5	1	1							(1 survivor Day 75)	
			39.0	>54.5		1	1		1	1					(4 survivors Day 75)	
			23.0	37			1			2	2	1			(2 survivors Day 75)	
	$N_3O_2Cl_2C_5H_9$		14.0	26			1	3	1		1		1		(1 survivor Day 75)	
	D		8.40	17		1	5	1								
		Every 7 days	39.0	31.5		1	1	1	1	1	1	1	1			
			23.0	64.5							1		1		1	5
			14.0	>75								(5 survivors Day 75)				3
			8.40	21		1	2	3			1	(1 survivor Day 75)				
			5.00	12		3										
		Daily	14.0	28.5			1		6	1						
			8.40	45.5							3	1	4			
			5.00	64								1	1			6
			3.00	24	1			5	1	1						
			1.80	11	3	5										
79037	Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso- (CCNU)	Single injection	108	>75						1					(7 survivors Day 75)	
			65.0	35.5		1	1	1		1	1				(3 survivors Day 75)	
			39.0	29.5		1			4	1	1	1				
	$N_3O_2ClC_9H_{16}$		23.0	15		4	2			1	1					
			14.0	12		7			1							
	E															
		Every 7 days	65.0	33			1	1	1	2		2		1		
			39.0	>75											(8 survivors Day 75)	
			23.0	17	1	3	1								(3 survivors Day 75)	
			14.0	16.5		4		1	1	1				1		
			8.40	10	6	2										
		Daily	23.0	26.5				3	5							
			14.0	56						1			2		5	
			8.40	31.5	1			1	2	1		1		1	(1 survivor Day 75)	
			5.00	12	4	1		3								
			3.00	11	3	5										
	Controls, expt inoc		—		10	8										
	Controls, expt inoc		—		9	8										

			3.00	11	3	5										
	Controls, expt inoc		—	16	8											
	Controls, expt inoc		—	9	8											
	Controls, 1/10 expt inoc		—	11.5		6										
	Controls, 1/100 expt inoc		—	14		4	2									
	Retransplant recipients		—	8	(from Day 6)	7	1									(10 survivors Day 75)
	Untreated without tumor		—	—												

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL–590[1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation)																	
				5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]benzoyl]- (methotrexate)	3.00	12							2	3	1			1				1			
		1.80	13.5								2	2	1	2						1		
		1.08	16.5								1			1	2	1				1	(2 survivors Day 23)	
		0.65	22				(2 survivors Day 23)							1					1	1	2	1
		0.39	8.5				4	1							1				1			1
	$N_8O_6C_{20}H_{22}$																					
	B																					
3052	1,9-Nonanediol, dimethanesulfonate	600	10.5						4	4												
		360	10.5						4	4												
		216	11							7	1											
	$O_6S_2C_{11}H_{24}$	130	11							6		1	1									
		78.0	10.5			1	1	1	1	1	1	2										
	E	47.0	9			2	1	4	1													
	p-Toluidine, α-inden-1-ylidene-*N*,*N*-dimethyl-	300†	8†				5	3														
		180	8				6	2														
		108	8			1	7															
	$NC_{13}H_{17}$	65.0	8			1	6	1														
		39.0	8			1	6	1														
	E																					
	Controls, expt inoc	—	8				7	1														
	Controls, expt inoc	—	8				6	2														
	Controls, 1/10 expt inoc	—	11							6												
	Controls, 1/100 expt inoc	—	12.5							1	2	2	1									
	Retransplant recipients	—	9.5		(from Day 5)							2	2	3	1							
	Untreated without tumor	—	—																			(10 survivors Day 23)

[1] CDBA male mice, 21–30 g per group; experimental inoc, 4,000,000 cells/mouse; daily sc treatment begun Day 5.
†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.
‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-596 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (days)	Mortality distribution (days after tumor implantation) 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	35
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-(methotrexate)	3.00	17									1	1	1	2		2	1									
		1.50*	27														1					1	1		3	2	
		0.75	25.5																	1	1		2	3	1		
		0.37	10				1	5						1												1	
	$N_8O_5C_{20}H_{22}$																										
	B																										
83083	*meso*-2,3-Butanediol, 1,4-bis[(di-2-chloro-1-methylethyl)[or(di-2-chloropropyl)]amino]-, dihydrochloride	10.0	14						1		3		3	1													
		5.00	10				1	6	1																		
		2.50	10				3	5																			
		1.25	9			2	3	3																			
		0.63	10				3	5																			
	$N_2O_2Cl_2C_{10}H_{22}$: 2 HCl																										
	D																										
80087	*p*-Toluidine, α-inden-1-ylidene-*N*,*N*-dimethyl-	833	10				3	5																			
		500	9.5			1	3	4																			
		300	9				5	3																			
	$NC_{18}H_{17}$	180	9			1	5	2																			
	E																										
	Controls, expt inoc	—	10				3	5																			
	Controls, expt inoc	—	9				7	1																			
	Controls, 1/10 expt inoc	—	11					1	4	1																	
	Controls, 1/100 expt inoc	—	14								1	3		1												1	
	Retransplant recipients	—	9.5 (from Day 6)										4	1	2		1										
	Untreated without tumor	—	—																(10 survivors Day 35)								

[1] BDF_1 male mice, 21–30 g per group; experimental inoc, 5,056,000 cells/mouse; daily sc treatment begun Day 6.

‡*See* footnote (‡) on page 23.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-607[1]

NSC No.	Compound, molecular formula, and vehicle‡	Daily dose (mg/kg)	Median survival time (mg/kg)	Mortality distribution (days after tumor implantation)																										
				6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	37	40	43	45	46
740	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]benzoyl]-(methotrexate)	3.00	18								1	1	1	1				2	2												
		1.80	20														3	2	1		1		1								
		1.08	22								2								2		1	1	2								
		0.65	22.5								3								1			1	1	1		1					
		0.39	17.5					2					1		1	1	2	1													
	$N_8O_8C_{20}H_{22}$																														
	B																														
68303	1,5-Pentanediamine, *N,N'*-bis-(2-chloroethyl)-, dihydrochloride	400†	11†					2	6																						
		200	10					6	2																						
		100	10				1	6																	1						
		50.0	10				2	6																							
	$N_2Cl_2C_6H_{20}$·2 HCl	25.0	9.5				4	4																							
	D																														
86056	Urea, 3-(1-adamantyl)-1-(2-chloroethyl)-1-nitroso-	100	24																1	1	2		2	1		1					
		50.0	32.5																			1		2		1	1	1	1	1	
		25.0	11					2	3	1		1														1					
	$N_3O_3ClC_{13}H_{20}$	12.5	10				2	4	2																						
		6.25	10				1	6	1																						
	E																														
	Controls, expt inoc	—	10				1	7																							
	Controls, expt inoc	—	10				1	7																							
	Controls, 1/10 expt inoc	—	11				1	1	3																						
	Controls, 1/100 expt inoc	—	12						1	4	1																				
	Retransplant recipients	—	9.5	(from Day 6)								1	3	3	1																
	Untreated without tumor	—	—																(10 survivors Day 46)												

[1]CDBA male mice, 23–30 g per group; experimental inoc, 4,096,000 cells/mouse; daily sc treatment begun Day 6.

‡*See* footnote (‡) on page 28.

†No clear evidence of toxicity appeared at any dose level tested, therefore the optimal dose may be higher than any tested.

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-618[1]

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-618 [1]

NSC No.	Compound, molecular formula, and vehicle‡	Treatment route	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation) 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
740	Glutamic acid, *N*-[p-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-(methotrexate)	sc	Daily	3.00	25.5				(2 survivors Day 32)											1				1			2			1			1		
				1.80	28				(1 survivor Day 32)													1								1	1	2		1	1
				1.08	26																						1	2	2		3				
				0.65	25																				1	1		6							
				0.39	23											1		1							1	3		1		1					
	$N_8O_6C_{20}H_{22}$																																		
	B																																		
40774	9*H*-Purine, 6-(methylthio)-9-β-D-ribofuranosyl-, dihydrate	Oral, with fasting	Daily	180	7				2	4	2																								
				108	9					1	1	3	3																						
				65.0	12.5									3	1	1	2		1																
				39.0	15								1			1	1	3		1		1													
	$N_4O_6SC_{11}H_{14}\cdot 2$ HOH			23.0	12								1	1	3	1		1	1																
	D	Oral, with fasting	Every 3 days	500	8						3																								
				300	8					2	4	2																							
				180	10.5						1	1	2	2		1	1																		
				108	16													2	3	3															
				65.0	13										2	3	2	1																	
		Oral, with fasting	Every 7 days	833	4		5	2				1																							
				500	6		2	1	2		1		1	1																						
				300	21												1		1			1		2		1	1					1			
				180	17													1	2	2				1		1	1								
				108	15.5								2	1				1	2	1				1											
		Oral, with fasting	Single injection	1388	4		3																												
				833	4		5											1		1	1														
				500	17.5														3	1	2	1		1											
				300	15.5												2	2	2		1	1													
				180	13									2	1	2	2	1																	
		ip	Daily	108	6			1	7																										
				65.0	9					1	1	3	3																						
				39.0	12									2	5				1																
				23.0	11								3	2	2		1																		
				14.0	11							1	2	5																					
		ip	Every 3 days	500	4		7		1																										
				300	6		2	2		3		1																							
				180	8.5		1	1			2	1		2		1																			
				108	16											1	1	1	2	2				1											
				65.0	16									2			1		3				1	1											
		ip	Every 7 days	500	4		3																												
				300	5		2	3	1					1			1																			
				180	17				1									1	2		1				1			2							
				108	14.5									2			2	2	1		1														
				65.0	11							1	1	4		1		1																	

TABLE 12.—Treatment of advanced leukemia L1210 in mice; summary of 32 experiments—Continued

Expt No. DL-618 [1]—Continued

NSC No.	Compound, molecular formula, and vehicle‡	Treatment route	Treatment schedule	Dose (mg/kg/injection)	Median survival time (days)	Mortality distribution (days after tumor implantation) 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
		ip	Single injection	500	4		8																											
				300	7.5		3	1					1					1	1			1												
				180	16.5									1				2	1	3				1										
				108	11.5								1	3	2	1	1																	
				65.0	11								3	3	2																			
	Controls, expt inoc			—	10							1	5	2														1		1				
	Controls, expt inoc			—	10							1	5	2																				
	Controls, 1/10 expt inoc			—	14.5												3	2	1															
	Controls, 1/100 expt inoc			—	22.5		(1 survivor Day 32)															1	2				1		1					
	Untreated without tumor			—			(8 survivors Day 32)																											

[1] BDF_1 male mice, 20–30 g per group; experimental inoc, 5,960,000 cells/mouse; treatment begun Day 3.

‡*See* footnote (‡) on page 23.

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Inhibitors of Nucleoside and Nucleotide Metabolism [1,2]

J. F. Henderson, A. R. P. Paterson, I. C. Caldwell, B. Paul, M. C. Chan, and K. F. Lau [3]

SUMMARY

A total of 164 purine and pyrimidine derivatives and analogs were tested in a search for inhibitors of nucleoside and nucleotide metabolism. The test systems were purine nucleotide biosynthesis de novo, adenine phosphoribosyltransferase, adenosine kinase, and nucleoside transport in human erythrocytes. A number of potent inhibitors of each system were identified.

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As part of an ongoing screening program to obtain preliminary indications of biochemical activity in purine and pyrimidine derivatives (1–3), we have searched for inhibitors of nucleoside and nucleotide metabolism. The principal source of candidate compounds has been the screening program of Drug Research and Development (formerly the Cancer Chemotherapy National Service Center), National Cancer Institute.

Each of the 164 compounds studied was tested first at a concentration of 1.0 mM for inhibitory activity in four systems: (*a*) purine biosynthesis de novo in Ehrlich ascites tumor cells incubated in vitro; (*b*) adenine phosphoribosyltransferase partially purified from Ehrlich ascites tumor cells; (*c*) adenosine kinase activity in extracts of Ehrlich ascites tumor cells; and (*d*) inosine synthesis by human erythrocytes in vitro (table 1). The latter assay, in which guanosine serves as a ribosyl donor, detects inhibitors of nucleoside transport.

The more active compounds, those which inhibited metabolism more than 50% in any of the assays, were retested at lower concentrations. Results are presented in table 2 (28 inhibitors of purine biosynthesis), table 3 (17 inhibitors of adenine phosphoribosyltransferase), table 4 (28 inhibitors of adenosine kinase), and table 5 (32 inhibitors of nucleoside transport).

SYSTEM I: PURINE BIOSYNTHESIS DE NOVO

Purine biosynthesis de novo was measured, as previously described (4), in tumor cells treated with azaserine to inhibit the enzyme phosphoribosylformylglycineamidine synthetase (EC 6.3.5.3), the fourth enzyme on this pathway. The amount of phosphoribosylformylglycineamide which accumulates because of this block is a measure of the rate of the early steps of this pathway. Decreases in the amount of this compound formed in the presence of test compounds were expressed in terms of percent inhibition. The enzymes frequently found to be inhibited in this test system are phosphoribosylpyrophosphate amidotransferase (EC 2.4.2.14) and ribose 5-phosphate pyrophosphokinase (EC 2.7.6.1).

Ehrlich ascites tumor cells (24 mg wet weight) were suspended in 2.0 ml of calcium-free Krebs-Ringer phosphate medium, containing 5.5 mM glucose, 2 mM glycine-^{14}C, 2 mM glutamine, 6.4 μM azaserine, and 1 mM test compound. Flasks were incubated at 37 C with shaking for 60 minutes in an air atmosphere. Phosphoribosylformylglycineamide was isolated by chromatography on Dowex-1-formate, and its total radioactivity measured. All incubation mixtures were prepared in duplicate and controls were run without added test compounds.

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[2] This work was supported by the Medical Research Council and National Cancer Institute of Canada.

[3] University of Alberta Cancer Research Unit (McEachern Laboratory) and Department of Biochemistry, Edmonton, Alberta, Canada.

Of the 28 active inhibitors of purine biosynthesis listed in tables 1 and 2, 15 were purine derivatives (out of 116 such compounds tested). Inhibitory activity was found in 9-hydroxymethylpurines additionally substituted at the 6 position by propylthio, butylthio, cyclopentylthio, and octylthio groups. In addition, two purine ribonucleosides substituted at the same position by phenylthio or 2-hydroxy-5-nitrobenzylthio groups were inhibitory. Several nucleosides in which sugar hydroxyl groups were substituted by formyl, acetyl, or ethylorthoacetate groups had inhibitory activity. The dinucleotide monophosphate, uridylyl-(3′→5′) adenosine, showed inhibitory activity.

Of the 35 compounds tested with ring systems analogous to purine, 12 were active. Two benzimidazole derivatives and several pyrrolo-[2,3-*d*]pyrimidines were of interest. In the latter group, the following substituents at the 4 position (comparable to the 6 position in purines) imparted activity: hydrogen, chloro, hydrazino, methylamino, methoxy, or methylthio groups.

SYSTEM II: ADENINE PHOSPHORIBOSYLTRANSFERASE

The initial velocity of the adenine phosphoribosyltransferase reaction was determined by measuring the synthesis of adenylate-^{14}C from phosphoribosylpyrophosphate and adenine-^{14}C, as described previously (2,5). The enzyme preparation used was partially purified from Ehrlich ascites tumor cells (5).

The incubation mixture contained enzyme (1.0 μg protein), 1 mM $MgSO_4$, 0.8 μM adenine labeled with ^{14}C, 6 μM phosphoribosylpyrophosphate, 0.18 M Tris-HCl buffer (pH 7.4), and 1 mM test compounds, in a total volume of 0.5 ml. This mixture was incubated for 12 minutes at 30 C. Reaction mixtures were extracted four times with 3 ml of water-saturated 1-butanol to remove unreacted ^{14}C-labeled adenine, and radioactive adenylate in the aqueous phase was measured. All tests were done in duplicate and control tests were run without added test compounds and without enzyme.

Twelve of 116 purine derivatives showed appreciable inhibitory effects (tables 1 and 3). Conversion of the ribose moieties of adenosine and guanosine to hydroxymethyldiglycolaldehydebisphenylhydrazones produced very active inhibitors. Likewise, both α and β anomers of 2′-deoxy-D-*erythro*-pentopyranosyl adenine were active, as were nucleosides or nucleoside analogs containing allopyranose, tetrahydropyran, mannofuranose, triacetylribose, methanol, or other substituents at the 9 position. Some substitution on the purine ring permitted activity, although adenine was the most effective base.

The 13 pyrimidine analogs and derivatives tested were not active, but the dinucleoside phosphate uridylyl-(3′→5′) adenosine was inhibitory.

Four of 35 purine and purine nucleoside analogs with substitution of ring atoms were considered active inhibitors. Two were benzimidazoles and two were pyrazolo [3,4-*d*]pyrimidines; all were substituted with rather bulky groups.

SYSTEM III: ADENOSINE KINASE

The inhibitory effects of test compounds on adenosine kinase activity were measured by comparing the amount of ^{14}C-labeled 6-methylthiopurine ribonucleoside that was phosphorylated in the presence and absence of the test compound (6,7). The phosphorylation requires adenosine triphosphate, and the enzyme preparation used was a sonic extract of Ehrlich ascites tumor cells.

Reaction mixtures in a total volume of 0.2 ml contained 2 to 3 milliunits of enzyme, 100 mM potassium succinate buffer (pH 5.4), 10 mM disodium adenosine triphosphate, 4 mM manganous chloride, 0.5 mM 6-(methylmercapto)purine ribonucleoside (^{14}C-methyl), and 1 mM test compounds. The reaction was started by the addition of enzyme, and, after 10 minutes incubation at 30 C, was stopped by heating for 4 minutes at 100 C. The product, 6-(methylmercapto)purine ribonucleoside 5′-phosphate, was isolated by chromatographing measured volumes of the reaction mixture on Whatman No. 1 paper in 5% sodium diphosphate; product radioactivity was measured. All tests were done in duplicate and control tests were run without added test compounds and without enzyme.

Tables 1 and 4 present the results of testing. Twelve of 116 purine derivatives were potent inhibitors, including three 6-dithio dimers of purine nucleosides containing different sugar

moieties. Several adenosine, inosine, and purine-6-thiol derivatives substituted at the 6 position with bulky groups were also inhibitory. As in systems I and II, uridylyl-(3′→5′)adenosine displayed inhibitory activity.

All but one of the 15 inhibitory purine and purine nucleoside analogs with substituted ring atoms were derivatives of pyrrolo[2,3-*d*]pyrimidine. Compounds of this class bearing chloro, amino, hydrazino, methoxy, methylamino, dimethylamino, and piperidino groups at the 4 position were inhibitory, and the further addition of iodo or bromo groups at the 5 position increased their potency. In contrast, derivatives containing 4-thio, methylthio, or oxo groups were inactive.

SYSTEM IV: NUCLEOSIDE TRANSPORT INTO CELLS

Purine and pyrimidine nucleosides enter animal cells (8,9) and human erythrocytes (10) by a carrier-mediated process. This process is inhibited by a group of purine ribonucleosides with particular substituent groups at the purine 6 position, as exemplified by 2-amino-6-(*p*-nitrobenzylthio)purine ribonucleoside (11,12). In the assay system presently used, nucleoside transport is necessarily involved and transport inhibitors are detected. When incubated with hypoxanthine, labeled at the 8 position with ^{14}C and guanosine, erythrocytes synthesize ^{14}C-8-inosine which appears in the medium. For this phosphorylase-mediated process to occur, guanosine must pass across the cell membrane. The assay also requires that the product pass outward through the membrane. Nucleoside passage in either direction across the red cell membrane is mediated and both processes are blocked by alkarylmercapto purine ribonucleosides (12).

Incubation mixtures contained 1.0 mM hypoxanthine labeled with ^{14}C, 1.0 mM guanosine, and 0.1 ml of human erythrocytes (washed cells from outdated, acid citrate-dextrose-stored blood) in a bicarbonate-buffered salts medium in a final volume of 1.0 ml. After incubation for 15 minutes at 37 C under O_2-5% CO_2, measured volumes of cell-free medium were chromatographed on paper to isolate the reaction product, inosine. Chromatogram sections were assayed directly for product radioactivity. All incubation mixtures were prepared in duplicate and control tests were run without added test compounds and without guanosine. Reaction mixtures of the same composition but with sonically disrupted erythrocytes were used under the same incubation conditions to test for possible inhibition of purine nucleoside phosphorylase. Such inhibition was not observed.

Tables 1 and 5 show that 23 of 116 purine derivatives tested were significantly inhibitory. In general, 9-alkyl or 9-β-D-ribofuranosyl purine derivatives with 6 position substitutes were active; inhibitory activity was not observed in purines without substitutions at the 9 position. Compounds bearing substituent groups on S, N, and O atoms located at the 6 position of the purine riboside were inhibitory to nucleoside transport; substituted benzyl groups imparted maximum inhibitory activity and less inhibitory were compounds bearing substituted phenyl and alkyl groups. Substitution at the 9 position by β-D-ribofuranosyl, propyl, and butyl moieties also caused inhibitory activity. An amino group at the 2 position of the purine derivatives was not essential for inhibitory activity.

None of the pyrimidine derivatives tested showed inhibitory activity, but nine compounds which were variously substituted analogs of the purine ring system were effective inhibitors. Two pyrazolo[3,4-*d*]pyrimidines substituted by isopentylamino and phenylethylamino groups showed moderate inhibitory activity. It is noteworthy that in this group, substitution by an alkyl or a β-D-ribose moiety at the 1 position (corresponding to the 9 position of purine) is not a requirement for inhibitory activity, as in the case of purine derivatives. Derivatives of 7-β-D-ribofuranosyl-pyrrolo[2,3-*d*]pyrimidine with substituents at the 4 or 5 (or both) positions showed moderate inhibitory activity. The 4 position could be substituted by methoxy, piperidyl, and benzylthio groups, and the 5 position by bromo and iodo groups.

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
			PURINE DERIVATIVES						
Adenine Derivatives									
98671	339	26315-51-5	Adenine, 9-(3-amino-3-deoxy-β-D-arabinofuranosyl)-	$N_6O_3C_{10}H_{14}$	B	5	6	6	0
105546	422	7724-76-7	Adenosine, N^6-(3-methyl-2-butenyl)-	$N_5O_4C_{15}H_{21}$	A	100	33	24	25
111357	350	—	Adenine, 2-methyl-7-β-D-ribofuranosyl-, monohydrate	$N_5O_4C_{11}H_{15}$ • HOH	E	18	5	−6	0
111359	348	17434-50-3	Adenine, 9-(2-deoxy-α-D-*erythro*-pentapyranosyl)-	$N_5O_3C_{10}H_{13}$	E	25	69	−9	3
111363	343	16755-05-8	Purine, 2-chloro-6-(1-piperidyl)-9-β-D-ribopyranosyl-, 2′,3′,4′-triacetate	$N_5O_7ClC_{21}H_{26}$	E	82	63	−4	0
111364	344	—	Purine, 6-(1-piperidyl)-9-β-D-ribopyranosyl-, 2′,3′,4′-triacetate, hemihydrate	$N_5O_7C_{21}H_{27}$ • ½HOH	E	16	3	−4	0
112511	353	19792-96-2	Adenosine, 5′-deoxy-5′-methanesulfonamido-	$N_6O_6SC_{11}H_{16}$	E	36	50	100	11
112514	356	—	Glucopyranoside, 6-amino-purin-8-yl-1-thio-, tetraacetate, β-D-	$N_5O_9SC_{23}H_{25}$	E	100	9	−20	5
112515	357	25253-77-4	Glucopyranoside, 6-amino-purin-8-yl-1-thio-, β-D-	$N_5O_5SC_{11}H_{15}$	E	0	19	−16	13
112524	364	21950-39-0	Adenosine, 5′-deoxy-2′,3′-O-isopropylidene-5′-methanesulfonamido-	$N_6O_6SC_{14}H_{20}$	E	44	8	9	37
112527	367	—	Adenosine, cyclic 2′,3′-(ethyl orthoacetate)	$N_5O_5C_{12}H_{17}$	E	100	34	100	30
112528	368	—	Adenosine, N^6-formyl-, 2′,3′-diformate 5′-p-toluenesulfonate	$N_5O_9SC_{20}H_{19}$	E	65	87	2	8
112852	419	—	Adenine, 9-[3-[L-α-(carboxyamino)hydrocinnamamido]-3-deoxy-β-D-arabinofuranosyl]-, benzyl ester	$N_7O_6C_{27}H_{29}$	A	2	33	12	2
113460	377	—	Adenine, 9-[3-[2-(carboxyamino)-5-(3-nitroguanidino)valeramido]-3-deoxy-β-D-arabinofuranosyl]-, benzyl ester, compd. with methanol (1:1), monohydrate	$N_{11}O_8C_{34}H_{41}$ • OCH_4 • HOH	A	12	−3	0	24
113547	378	16033-27-5	Purine, 2,6-bis(hydroxyamino)-	$N_6O_2C_5H_6$	A	38	2	−4	0
113941	381	—	Adenine, 9-(2-deoxy-β-D-*erythro*-pentapyranosyl)-	$N_5O_3C_{10}H_{13}$	A	3	62	−6	0
113989	393	7697-49-6	Adenine, N^9-(2-imidazol-4-yl-ethyl)-, hemihydrate	$N_7C_{10}H_{11}$ • ½ HOH	A	38	42	−2	11
114009	399	18520-81-5	Adenine, 9-α-D-arabinopyranosyl-, 2′,3′,4′-triacetate	$N_5O_7C_{16}H_{19}$	A	7	−2	−2	10
114010	400	—	Adenine, 9-[3-(L-α-aminohydrocinnamamido)-3-deoxy-β-D-arabinofuranosyl]-, sesquihydrate	$N_7O_4C_{19}H_{23}$ • 1½ HOH	A	1	−19	7	0
114860	407	28361-09-3	Adenine, 9-β-D-allopyranosyl-	$N_5O_5C_{11}H_{15}$	A	18	70	16	0
114861	408	—	Adenine, 9-α-D-talopyranosyl-	$N_5O_5C_{11}H_{15}$	A	8	18	10	5
114862	409	—	Adenine, 9-α-D-mannopyranosyl-	$N_5O_5C_{11}H_{15}$	A	2	43	10	4
114911	410	—	Adenine, 9-[3-[2-(carboxyamino)propionamido]-3-deoxy-β-D-arabinofuranosyl]-, benzyl ester, hydrate (4:3)	$N_7O_6C_{21}H_{23}$ • ⅔ HOH	A	8	3	2	3
114912	411	—	Adenine, 9-[3-[L-2,6-bis(carboxyamino)-hexanamido]-3-deoxy-β-D-arabinofuranosyl]-, dibenzyl ester	$N_9O_8C_{35}H_{38}$	A	0	42	5	25
115605	415	—	Adenine, 9-[3-(L-2-aminopropionamido)-3-deoxy-β-D-arabinofuranosyl]-, monohydrate	$N_7O_4C_{13}H_{15}$ • HOH	A	−3	−1	12	5

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
115606	416	—	Adenine, 9-[3-deoxy-3-(L-2,6-diaminohexanamido)-β-D-arabinofuranosyl]-, hemihydrate	$N_8O_4C_{16}H_{20} \cdot \frac{1}{2}$ HOH	A	0	−16	7	2
116931	423	—	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α′-(hydroxymethyl)-, bis(phenylhydrazone)	$N_9O_2C_{22}H_{22}$	A	100	99	−6	23
117842	433	15645-46-2	9*H*-Purine, 2-amino-8-chloro-6-(methylamino)-9-β-D-ribofuranosyl-	$N_6O_4ClC_{11}H_{15}$	A	16	16	−11	7
117843	434	15717-47-2	9*H*-Purine, 2-amino-8-chloro-6-(dimethylamino)-9-β-D-ribofuranosyl-	$N_6O_4ClC_{12}H_{17}$	A	27	43	−22	13
117844	435	15717-48-3	9*H*-Purine, 2-amino-8-chloro-6- piperidino-9-β-D-ribofuranosyl-	$N_6O_4ClC_{15}H_{21}$	A	18	2	−13	15
118425	453	18031-20-4	Adenine, 9-α-D-xylopyranosyl-	$N_5O_4C_{10}H_{13}$	A	−3	11	9	0
118426	454	18031-19-1	Adenine, 9-β-D-arabinopyranosyl-	$N_5O_4C_{10}H_{13}$	A	33	32	7	6
118427	455	20847-09-0	Acetic acid, trifluoro-, compd. with 8-bromoadenosine 5′-acetate (1:1)	$O_2F_3C_2H \cdot N_5O_5BrC_{12}H_{14}$	A	17	26	10	37
119661	464	10279-89-7	Adenine, 9-β-D-allofuranosyl-	$N_5O_4C_{11}H_{13}$	A	13	41	29	3
119662	465	10279-87-5	Adenine, 9-β-D-gulofuranosyl-	$N_5O_4C_{11}H_{13}$	A	0	20	4	0
119663	466	10279-88-6	Adenine, 9-β-L-gulofuranosyl-	$N_5O_4C_{11}H_{13}$	A	−3	9	−5	0
119664	467	—	Adenine, 9-α-D-mannofuranosyl-	$N_5O_4C_{11}H_{13}$	A	24	87	−3	0
119843	468	—	Adenosine, 5′-azido-2′,5′-dideoxy-	$N_8O_2C_{10}H_{12}$	A	27	47	2	11
—	558	—	Adenosine, N^6-benzyl-	$N_5O_4C_{17}H_{19}$	D	25	4	53	99
—	560	—	Adenosine, N^6-methyl-N^6-(*p*-nitrobenzyl)-	$N_6O_6C_{18}H_{20}$	E	12	3	57	100
—	562	—	Adenosine, N^6-(*p*-nitrobenzyl)-	$N_6O_6C_{17}H_{18}$	D	−19	17	55	100
Guanine Derivatives									
112521	361	19039-33-9	Inosine, 1,2-diamino-	$N_6O_5C_{10}H_{14}$	E	24	19	−6	0
112522	362	19029-70-0	Purine-6,8(1*H*,9*H*)-dione, 1,2-diamino-9-β-D-ribofuranosyl-	$N_6O_6C_{10}H_{14}$	E	7	3	−11	2
112853	420	—	Guanine, N^2-acetyl-9-β-D-xylopyranosyl-, 2′,3′,4′-triacetate, compd. with CCl_4 (10:9)	$N_5O_8C_{23}H_{27} \cdot \frac{9}{10}$ (Cl_4C)	A	46	29	−2	3
115607	417	—	Guanine, 9-β-D-xylofuranosyl-	$N_5O_5C_{10}H_{13}$	A	8	−52	4	3
116932	424	—	Diglycolaldehyde, α-(2-amino-6-hydroxy-9*H*-purin-9-yl)-α′-(hydroxymethyl)-, bis-(phenylhydrazone)	$N_9O_3C_{22}H_{22}$	A	10	54	−2	7
119169	457	20789-67-7	9*H*-Purine-6(1*H*)-thione, 2-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-	$N_5O_3SC_{11}H_{13}$	A	−42	10	72	6
119846	470	27964-07-4	Purine-6,8(1*H*,9*H*)-dione, 2-amino-1-methyl-9-β-D-ribofuranosyl-	$N_5O_6C_{11}H_{15}$	A	−9	9	−11	4
119847	471	27963-76-4	Guanosine, 8-(benzyloxy)-1-methyl-	$N_5O_6C_{18}H_{21}$	A	−6	14	−4	7
119848	472	19029-69-7	Inosine, 1,2-diamino-8-(benzyloxy)-	$N_6O_6C_{17}H_{20}$	A	−18	17	0	7
119850	473	19029-67-5	Inosine, 1,2-diamino-2′-deoxy-	$N_6O_4C_{10}H_{14}$	A	19	18	−8	0
119855	475	—	Guanosine, 5′-azido-5′-deoxy-	$N_8O_4C_{10}H_{12}$	A	50	13	−11	2
Hypoxanthine Derivatives									
109320	372	13389-16-7	Inosine, 8-amino-	$N_5O_5C_{10}H_{13}$	A	75	8	3	−36
112523	363	20419-69-6	Purine, 2,6-diethoxy-	$N_4O_2C_9H_{12}$	E	7	9	−4	30
112525	365	—	Hypoxanthine, 8-bromo-	$N_4OBrC_5H_3$	E	7	3	0	7

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
113948	388	29836-04-2	Purine-6,8(1*H*,9*H*)-dione, 9-β-D-ribofuranosyl-8-thio-	$N_4O_5SC_{10}H_{12}$	A	17	11	3	0
113949	389	2104-65-6	Inosine, 8-(methylthio)-	$N_4O_5SC_{11}H_{14}$	A	0	13	2	6
113950	390	—	Inosine, 8-methoxy-	$N_4O_6C_{11}H_{14}$	A	0	5	2	0
118207	437	—	Hypoxanthine, 2-[(*o*-nitrobenzyl)thio]-	$N_5O_3SC_{11}H_9$	A	39	9	−12	0
118208	438	—	Hypoxanthine, 2-[(*m*-nitrobenzyl)thio]-	$N_5O_3SC_{11}H_9$	A	22	24	3	0
118209	439	—	Hypoxanthine, 8-[(*o*-nitrobenzyl)thio]-	$N_5O_3SC_{11}H_9$	A	−1	17	7	0
118210	440	—	Hypoxanthine, 8-[(*m*-nitrobenzyl)thio]-	$N_5O_3SC_{11}H_9$	A	−2	8	2	0
118211	441	—	Hypoxanthine, 8-[(*m*-aminobenzyl)thio]-	$N_5OSC_{11}H_{11}$	A	−6	15	−13	6
119851	474	19029-66-4	Inosine, 1-amino-	$N_5O_5C_{10}H_{13}$	A	43	6	−5	0
—	559	—	Inosine, O²-benzyl-	$N_4O_5C_{17}H_{18}$	D	3	3	76	98
6-Mercaptopurine Derivatives									
55467	568	—	9*H*-Purine, 6-[(2-methyl-1-naphthyl)methylthio]-9-β-D-ribofuranosyl-	$N_4O_4SC_{22}H_{22}$	A	−24	8	−12	86
86810	394	—	Benzenearsonic acid, *p*-([6-(2-thenylthio)-purin-8-yl]-azo)-	$N_6O_5S_2AsC_{16}H_{13}$	A	88	94	−7	36
99930	395	14133-12-1	9*H*-Purine-9-methanol, 6-(octylthio)-	$N_4OSC_{14}H_{22}$	A	62	23	5	0
99931	396	14133-17-6	Carbamic acid, butyl-, [6-(propylthio)-9*H*-purin-9-yl]methyl ester	$N_5O_2SC_{14}H_{21}$	A	29	9	7	24
99935	397	14196-96-4	9*H*-Purine-9-methanol, 6-(cyclopentylthio)-	$N_4OSC_{11}H_{14}$	A	100	47	3	32
99943	398	—	9*H*-Purine-9-methanol, 6-[(4-hydroxy-2-butynyl)thio]-	$N_4O_2SC_{10}H_{10}$	A	0	90	11	3
111356	351	20187-89-7	Purine-6(1*H*)-thione, 7-β-D-ribofuranosyl-	$N_4O_4SC_{10}H_{12}$	E	22	8	2	8
111361	346	20290-88-4	Purine-6(1*H*)-thione, 9-(2-deoxy-α-D-*erythro*-pentopyranosyl)-	$N_4O_3SC_{10}H_{12}$	E	35	−47	2	0
111362	345	20350-17-8	Purine-6(1*H*)-thione, 9-(2-deoxy-β-D-*erythro*-pentopyranosyl)-	$N_4O_3SC_{10}H_{12}$	E	15	−30	15	0
111572	373	—	Barbituric acid, 5-ethyl-5-[(9-β-D-ribofuranosyl-9*H*-purin-9-yl)thio]-	$N_6O_7SC_{16}H_{18}$	A	13	21	13	3
111702	371	—	*p*-Dioxane-2-methanol, 3,5-dihydroxy-6-[6-(methylthio)-9*H*-purin-9-yl]-	$N_4O_6SC_{11}H_{14}$	A	20	2	31	11
113617	426	23521-02-0	9*H*-Purine, 6,6′-dithiobis-[9-β-D-arabinofuranosyl-	$N_8O_8S_2C_{20}H_{22}$	A	−7	13	65	0
114334	401	14196-95-3	9*H*-Purine-9-methanol, 6-(butylthio)-	$N_4OSC_{10}H_{14}$	A	100	18	−9	60
114335	402	14133-10-9	9*H*-Purine-9-methanol, 6-(hexylthio)-	$N_4OSC_{12}H_{18}$	A	26	6	−7	9
114336	403	—	Carbamic acid, methyl-, [6-(propylthio)-9*H*-purin-9-yl]methyl ester	$N_5O_2SC_{11}H_{15}$	A	5	−21	−9	26
114337	404	—	9*H*-Purine-9-methanol, 8-methyl-6-(propylthio)-	$N_4OSC_{10}H_{14}$	A	82	−22	1	45
114913	412	18520-87-1	9*H*-Purine-6-thiol, 9-α-D-arabinopyranosyl-, 2′,3′,4′-triacetate	$N_4O_7SC_{16}H_{18}$	A	0	−4	0	6
115603	413	—	9*H*-Purine-6-thiol, 9-β-D-arabinopyranosyl-, compd. with methanol (3:1)	$N_4O_4SC_{10}H_{12}\cdot\frac{1}{2}(OCH_4)$	A	10	−23	2	4
115604	414	18520-79-1	9*H*-Purine-6-thiol, 9-α-D-arabinopyranosyl-	$N_4O_4SC_{10}H_{12}$	A	0	35	7	0
118612	456	—	9*H*-Purine, 6,6′-dithiobis-[9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-, monohydrate	$N_8O_8S_2C_{20}H_{22}\cdot HOH$	A	10	9	88	5

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
119857	477	6974-67-0	Purine-6-thiol, 8-amino-	$N_5SC_5H_5$	A	8	37	−2	2
119983	479	—	9*H*-Purine, 6,6′-dithiobis-[2-amino-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-, hydrate (3:11)	$N_{10}O_6S_2C_{20}H_{22}$ • 3 ⅔ HOH	A	−11	15	88	89
119984	480	26326-58-9	9*H*-Purine, 6,6′-dithiobis-[2-amino-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-	$N_{10}O_6S_2C_{20}H_{24}$	A	−50	13	39	0
—	553	—	9*H*-Purine, 6-[(2-hydroxy-5-nitrobenzyl) thio]-9-β-D-ribofuranosyl-	$N_5O_7SC_{17}H_{17}$	D	85	51	80	93
—	554	—	9*H*-Purine, 6-[(*p*-nitrobenzyl) thio]-9-β-D-ribofuranosyl-	$N_5O_6SC_{17}H_{17}$	D	2	2	−12	92
—	556	—	9*H*-Purine, 6-[(*p*-nitrophenyl) thio]-9-β-D-ribofuranosyl-	$N_5O_6SC_{16}H_{15}$	D	−62	3	−6	100
—	557	—	9*H*-Purine, 6-(phenylthio)-9-β-D-ribofuranosyl-	$N_4O_4SC_{16}H_{16}$	D	100	3	5	86
6-Thioguanine Derivatives									
44584	304	—	9*H*-Purine, 2-amino-6-(1-methyl-4-nitroimidazol-5-ylthio)-9-propyl-	$N_8O_2SC_{12}H_{14}$	A	−40	0	14	17
46386	338	—	9*H*-Purine, 2-amino-6-[(6-methyl-2-pyridyl)-methylthio]-9-β-D-ribofuranosyl-	$N_6O_4SC_{17}H_{20}$	A	−57	4	−1	27
46389	564	—	Acetophenone, 2-[(2-amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl) thio]-4′-chloro-	$N_5O_5SClC_{18}H_{18}$	A	−51	31	−3	25
46390	565	—	Acetophenone, 2-[(2-amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl) thio]-	$N_5O_5SC_{18}H_{19}$	A	−45	5	−13	51
46391	566	13153-20-3	9*H*-Purine, 2-amino-6-(butylthio)-9-β-D-ribofuranosyl-	$N_5O_4SC_{14}H_{21}$	A	−27	6	−1	100
47778	302	—	9*H*-Purine, 2-amino-6-(isopropylthio)-9-propyl-	$N_5SC_{11}H_{17}$	A	41	−1	4	85
47780	314	—	9*H*-Purine, 2-amino-9-butyl-6-(isopropylthio)-	$N_5SC_{12}H_{19}$	A	−2	3	8	93
47785	567	—	9*H*-Purine, 2-amino-6-(isopropylthio)-9-β-D-ribofuranosyl-	$N_5O_4SC_{13}H_{19}$	A	−7	7	−7	92
48719	326	—	9*H*-Purine, 2-amino-9-isobutyl-6-(propylthio)-	$N_5SC_{12}H_{19}$	A	15	25	14	100
51470	307	—	Acetic acid, (2-amino-9-propyl-9*H*-purin-6-ylthio)-	$N_5O_2SC_{10}H_{13}$	A	−44	3	0	4
51471	305	—	9*H*-Purine, 2-amino-9-propyl-6-[(2-pyridylmethyl) thio]-	$N_6SC_{14}H_{16}$	A	4	3	0	93
51477	328	—	9*H*-Purine, 2-amino-9-(2-methylbutyl)-6-(2-pyridylmethylthio)-	$N_6SC_{16}H_{20}$	A	−3	5	5	100
54266	337	—	9*H*-Purine, 2-amino-6-[(*p*-fluorobenzyl) thio]-9-β-D-ribofuranosyl-	$N_5O_4SFC_{17}H_{18}$	A	21	7	0	100
55468	569	—	9*H*-Purine, 2-amino-6-(sec-butylthio)-9-β-D-ribofuranosyl-	$N_5O_4SC_{14}H_{21}$	A	−9	11	−12	100
55469	570	6944-09-8	9*H*-Purine, 2-amino-6-(ethylthio)-9-β-D-ribofuranosyl-	$N_5O_4SC_{12}H_{17}$	A	−46	32	−6	83
119656	463	—	9*H*-Purine, 6,6′-dithiobis-[2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-, hydrate (3:5)	$N_{10}O_6S_2C_{20}H_{24}$ • 1 ⅔ HOH	A	19	11	74	0
119845	469	—	Purine-6,8(1*H*,9*H*)-dione, 2-amino-1-methyl-9-β-D-ribofuranosyl-6-thio-	$N_5O_5SC_{11}H_{13}$	A	5	8	−5	2
—	555	—	9*H*-Purine, 2-amino-6-[(2-hydroxy-5-nitrobenzyl) thio]- 9-β-D-ribofuranosyl-	$N_6O_7SC_{17}H_{18}$	D	−7	33	50	96
Miscellaneous Purine Derivatives									
88182	425	3510-73-4	9*H*-Purine, 6-chloro-9-β-D-ribofuranosyl-, 2′,3′,5′-tribenzoate	$N_4O_7ClC_{31}H_{23}$	A	21	28	−3	0

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
112526	366	20419-68-4	9*H*-Purine, 2,6-dichloro-9-(tetrahydropyran-2-yl)-	$N_4OCl_2C_{10}H_{10}$	E	23	99	−7	23
113491	418	4902-17-4	Theophylline, 7,7′-(1,4-piperazinediyldimethylene)di-	$N_{10}O_4C_{20}H_{28}$	A	0	−2	10	14
114754	405	4921-56-6	Theobromine, 8-(chloromethyl)-	$N_4O_2ClC_8H_9$	A	53	26	−4	6
114755	406	—	Theobromine, 8-(hydroxymethyl)-	$N_4O_3C_8H_{10}$	A	0	−132	12	3
117841	432	13389-08-7	Xanthosine, 8-amino-	$N_5O_6C_{10}H_{13}$	A	19	−3	−8	0
118092	436	3256-24-4	Adenosine, uridylyl-(3′→5′)-	$N_7O_{12}PC_{19}H_{24}$	A	85	97	99	0
			PYRIMIDINE DERIVATIVES						
98948	340	7481-90-5	Thymine, 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-	$N_2O_4C_{10}H_{12}$	C	12	5	1	0
112512	354	16710-12-6	Cytidine, 6-methyl-	$N_3O_5C_{10}H_{15}$	E	1	8	−7	4
112513	355	16710-13-7	Uridine, 6-methyl-	$N_2O_6C_{10}H_{14}$	E	12	10	−1	2
112520	360	23537-54-4	Uracil, 6-(methylthio)-3-β-D-ribofuranosyl-	$N_2O_5SC_{10}H_{14}$	E	−37	12	−8	2
113552	370	—	Thymidine, thymidylyl-(5′→3′)-, ester with hydracrylonitrile, mixt. with thymidylyl-(3′→3′) thymidine, ester with hydracrylonitrile (24:1)	$N_5O_{12}PC_{23}H_{30}$	A	0	13	−15	20
114742	421	—	Uracil, 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5-fluoro-	$N_2O_4FC_9H_9$	A	15	18	6	0
119172	458	20105-52-6	D-*erythro*-Pentofuranuronic acid, 1,2-dideoxy-1-(5-fluoro-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-, butyl ester, β-	$N_2O_6FC_{13}H_{17}$	A	28	7	10	0
119173	459	20105-73-1	D-*erythro*-Pentofuranuronic acid, 1,2-dideoxy-1-(5-fluoro-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-, 2-chloroethyl ester, β-	$N_2O_6ClFC_{11}H_{12}$	A	12	17	12	0
119174	460	20105-72-0	D-*erythro*-Pentofuranuronic acid, 1,2-dideoxy-1-(5-fluoro-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-, dodecyl ester, β-	$N_2O_6FC_{21}H_{33}$	A	27	12	16	3
119175	461	—	D-*erythro*-Pentofuranuronamide, 1,2-dideoxy-1-(5-fluoro-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-N-1-naphthyl-, β-	$N_3O_5FC_{19}H_{16}$	A	33	2	17	0
119176	462	20105-70-8	D-*erythro*-Pentofuranuronic acid, 1,2-dideoxy-1-(5-fluoro-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-, methyl ester, β-	$N_2O_6FC_{10}H_{11}$	A	−5	14	10	0
518132	341	13957-31-8	Uridine, 4-thio-	$N_2O_5SC_9H_{12}$	E	20	8	1	6
			PURINE AND PURINE NUCLEOSIDE ANALOGS WITH SUBSTITUTION OF RING ATOMS						
			Benzimidazole Derivatives						
111354	342	—	Benzimidazole, 2-chloro-1-β-D-ribofuranosyl-, hemihydrate	$N_2O_4ClC_{12}H_{13} \cdot ½\ HOH$	E	21	10	5	0
111355	352	—	Benzimidazole, 2-thio-1-β-D-ribofuranosyl-	$N_2O_4SC_{12}H_{14}$	E	0	10	−9	8
111358	349	4857-06-1	Benzimidazole, 2-chloro-	$N_2ClC_7H_5$	E	89	10	4	0
112742	369	13083-37-9	Benzimidazole, 2-thio-1-[2-(4-pyridyl)ethyl]-	$N_3SC_{14}H_{13}$	E	54	85	−6	11
113944	384	22424-28-8	Benzimidazole, 2-(methylthio)-1-β-D-ribofuranosyl-	$N_2O_4SC_{13}H_{16}$	A	36	0	14	5
113945	385	22416-77-9	Benzimidazole, 2-piperidino-1-β-D-ribofuranosyl-	$N_3O_4C_{17}H_{23}$	A	1	−10	0	0

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
113946	386	22416-78-0	Benzimidazole, 2-morpholino-1-β-D-ribofuranosyl-	$N_3O_5C_{16}H_{21}$	A	0	4	15	0
113947	387	22416-76-8	Benzimidazole, 2-methoxy-1-β-D-ribofuranosyl-	$N_2O_5C_{12}H_{14}$	A	6	11	7	0
113987	392	—	1,2,3,4-Butanetetrol, 1,4-bis(5-chloro-2-benzimidazolyl)-, dimethanesulfonate, D-manno-	$N_4O_4Cl_2C_{22}H_{26} \cdot 2\,(O_3SCH_4)$	A	0	94	2	0
1-*H*-Pyrazolo-[3,4-*d*]pyrimidine Derivatives									
11607	374	—	1*H*-Pyrazolo[3,4-*d*]pyrimidine, 4-isopentylamino-, hydrochloride	$N_5C_{10}H_{15} \cdot HCl$	A	5	69	42	74
11641	375	—	1*H*-Pyrazolo[3,4-*d*]pyrimidine,4-phenethylamino-, hydrochloride	$N_5C_{12}H_{13} \cdot HCl$	A	28	86	60	91
117835	427	—	1*H*-Pyrazolo[3,4-*d*]pyrimidine-3-carbonitrile, 4-amino-1-methyl-	$N_6C_7H_6$	A	31	27	3	4
Pyrazolo[3′,4′:5,4]pyrrolo[2,3-*d*]pyrimidine Derivative									
117837	429	22256-93-5	Pyrazolo[3′,4′:5,4]pyrrolo[2,3-*d*]pyrimidine, 3,4-diamino-1,8-dihydro-8-β-D-ribofuranosyl-	$N_7O_4C_{12}H_{13}$	A	31	33	0	8
Pyrido[2,3-*d*]pyrimidine Derivatives									
112518	358	24410-19-3	Pyrido[2,3-*d*]pyrimidine-4(3*H*)-one	$N_3OC_7H_5$	E	13	19	−6	4
112519	359	21038-66-4	Pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione	$N_3O_2C_7H_5$	E	5	19	−2	5
7*H*-Pyrrolo[2,3-*d*]pyrimidine Derivatives									
99439	442	69-34-1	7*H*-Pyrrolo(2,3-*d*]pyrimidine-4-one, 3,7-dihydro-7-β-D-ribofuranosyl-	$N_3O_5C_{11}H_{12}$	E	−28	2	7	50
100278	443	2864-21-3	7*H*-Pyrrolo[2,3-*d*]pyrimidine-4-thiol, 7-β-D-ribofuranosyl-	$N_3O_4SC_{11}H_{13}$	E	1	1	3	59
100279	444	20371-00-0	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-(dimethylamino)-7-β-D-ribofuranosyl-	$N_4O_4C_{13}H_{19}$	E	100	2	62	23
101159	445	16754-85-1	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-(benzylthio)-7-β-D-ribofuranosyl-	$N_2O_4SC_{18}H_{19}$	E	56	−3	66	97
101160	446	16754-81-7	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-methoxy-7-β-D-ribofuranosyl-	$N_2O_5C_{12}H_{15}$	E	90	3	68	68
103791	447	13241-46-8	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-(methylamino)-7-β-D-ribofuranosyl-	$N_4O_4C_{12}H_{16}$	E	95	2	67	10
103798	448	16754-82-8	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-piperidino-7-β-D-ribofuranosyl-	$N_4O_4C_{16}H_{22}$	E	−3	8	63	88
105826	449	16754-86-2	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-(methylthio)-7-β-D-ribofuranosyl-	$N_2O_4SC_{12}H_{15}$	E	94	3	9	0
107519	450	16754-83-9	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 7-β-D-ribofuranosyl-	$N_2O_4C_{11}H_{12}$	E	97	−7	89	13
111360	347	—	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-hydrazino-7-β-D-ribofuranosyl-	$N_5O_4C_{11}H_{15}$	E	100	−45	86	7
113939	379	24386-93-4	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-amino-5-iodo-7-β-D-ribofuranosyl-	$N_4O_4IC_{11}H_{13}$	A	44	17	100	75
113940	380	24386-91-2	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-chloro-5-iodo-7-β-D-ribofuranosyl-	$N_2O_4ClIC_{11}H_{11}$	A	41	5	98	94
113942	382	24386-90-1	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 5-bromo-4-(methylthio)-7-β-D-ribofuranosyl-	$N_2O_4SBrC_{12}H_{14}$	A	100	6	100	94

TABLE 1.—Screening for inhibitors of nucleoside and nucleotide metabolism—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Inhibition (%) when analog concentration was 1.0 mM in these test systems: I	II	III	IV
113943	383	20201-56-3	7*H*-Pyrrolo[2,3-*d*]pyrimidine-5-carboxamide, 4-amino-6-bromo-7-β-D-ribofuranosyl-	$N_4O_5BrC_{12}H_{14}$	A	36	5	53	0
113951	391	20201-5502	7*H*-Pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile, 4-amino-6-bromo-7-β-D-ribofuranosyl-	$N_4O_4BrC_{12}H_{12}$	A	0	14	56	3
117836	428	—	7*H*-Pyrrolo[2,3-*d*]pyrimidine-5-carboxamid-oxime, 4-amino-6-bromo-7-β-D-ribofuranosyl-	$N_5O_5BrC_{12}H_{15}$	A	59	24	37	6
117838	430	—	7*H*-Pyrrolo[2,3-*d*]pyrimidine-5-carboxamide, 4-amino-6-(methylthio)-7-β-D-ribofuranosyl-	$N_4O_5SC_{13}H_{17}$	A	4	21	79	10
117839	431	—	7*H*-Pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile, 4-chloro-7-β-D-ribofuranosyl-	$N_4O_4ClC_{12}H_{11}$	A	97	11	100	29
2*H*-Pyrrolo[3,2-*d*]pyrimidine Derivatives									
119856	476	20419-74-3	2*H*-Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*)-dione, 7-bromo-3,5-dihydro-	$N_3O_2BrC_6H_4$	A	13	17	−1	8
119865	478	20419-75-4	2*H*-Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*)-dione, 6,7-dibromo-3,5-dihydro-	$N_3O_2Br_2C_6H_3$	A	42	37	−9	5

*The source of each compound is coded as follows:

Code	Source
A	Drug Research and Development National Cancer Institute Bethesda, Md
B	Dr. Leon Goodman Stanford Research Institute Menlo Park, Calif
C	Dr. J. P. Horowitz Michigan Cancer Foundation Detroit, Mich
D	University of Alberta Cancer Research Unit Edmonton, Alberta, Canada
E	Dr. R. K. Robins ICN Nucleic Acid Research Institute Irvine, Calif

TABLE 2.—Inhibitors of purine biosynthesis de novo (compounds active in System I when tested at a concentration of 1 mM): further testing in System I

Compound		Inhibition (%) at these concentrations (mM):		
NSC No.	CRU No.	1.0	10^{-1}	10^{-2}
PURINE DERIVATIVES				
86310	394	88	23	
99930	395	62	−19	
99935	397	100	30	−7
105546	422	100	93	8
109320	372	75	52	−6
112514	356	100	−23	
112527	367	100	31	19
112528	368	65	−5	
114334	401	100	30	−7
114337	404	82	30	
114754	405	53	14	
116931	423	100	65	45
118092	436	85	21	
119855	475	50	20	
	553	85	36	
	557	100	86	36
PURINE AND PURINE NUCLEOSIDE ANALOGS WITH SUBSTITUTION OF RING ATOMS				
101159	445	56	9	
100279	444	100	88	24
101160	446	90	83	31
103791	447	95	83	33
105826	449	94	69	28
107519	450	97	71	8
111358	349	89	14	
111360	347	100	98	13
112742	369	55	25	
113942	382	100	39	
117836	428	59	39	
117839	431	97	58	27

TABLE 8.—Inhibitors of adenine phosphoribosyltransferase (compounds active in System II when tested at a concentration of 1 mM): further testing in System II

Compound		Inhibition (%) at these concentrations (mM):			
NSC No.	CRU No.	1.0	10^{-1}	10^{-2}	10^{-3}
PURINE DERIVATIVES					
86310	394	99	2		
99943	398	90	0		
111359	348	68	10		
111363	343	63	0		
112511	353	50	0		
112526	366	99	2		
112528	368	87	1		
113941	381	62	7		
114860	407	70	13		
116931	423	99	97	75	13
116932	424	54	4		
118092	436	97	38		
119664	467	87	47		
PURINE AND PURINE NUCLEOSIDE ANALOGS WITH SUBSTITUTION OF RING ATOMS					
11607	374	69	18		
11641	375	86	6		
112742	369	85	5		
113987	392	94	4		

TABLE 4.—Inhibitors of adenosine kinase (compounds active in System III when tested at a concentration of 1 mM): further testing in System III

Compound		Inhibition (%) at these concentrations (mM):			
NSC No.	CRU No.	1.0	10^{-1}	10^{-2}	10^{-3}
PURINE DERIVATIVES					
112511	353	100	8		
112527	367	100	10		
113617	426	65	34		
118092	436	99			
118612	456	88	58	−3	
119169	457	72	8		
119983	479	88	58	−2	
	553	80	−13		
	555	50	−3		
	558	53	−10		
	559	76	5		
	560	57	13		
	562	55	−1		
PURINE AND PURINE NUCLEOSIDE ANALOGS WITH SUBSTITUTION OF RING ATOMS					
11641	375	60	−13		
100279	444	62	−8		
101159	445	66	27		
101160	446	68	45		
103791	447	67	40		
103798	448	63	15		
107519	450	89	60	−8	
111360	347	86	24	17	
113939	379	100	94	91	63
113940	380	98	93	89	67
113942	382	100	93	65	28
113943	383	53	18		
113951	391	56	16		
117838	430	79	38		
117839	431	100	87	19	

TABLE 5.—Inhibitors of nucleoside transport (compounds active in System IV when tested at a concentration of 1 mM): further testing in System IV

Compound		Inhibition (%) at these concentrations (mM):			
NSC No.	CRU No.	1.0	10^{-1}	10^{-2}	10^{-3}
PURINE DERIVATIVES					
46390	565	51	15	2	
46391	566	83	17	3	
47778	302	85	17	1	
47780	314	93	19	2	
47785	567	92	11	2	
48719	326	100	36	3	
51471	305	93	33	10	
51477	328	100	55	6	
54266	337	100	100	85	23
55467	568	86	29	6	
55468	569	100	43	5	
114334	401	60	1		
119983	479	89	14	−4	
	553	95	93	92	96
	554	92	90	90	99
	555	96	96	95	94
	556	100	98	83	55
	557	86	32	4	3
	558	99	86	25	5
	559	98	98	72	19
	560	100	100	96	87
	562	100	100	100	94
PURINE AND PURINE NUCLEOSIDE ANALOGS WITH SUBSTITUTION OF RING ATOMS					
11607	374	74	9	0	
11641	375	91	21	0	
100278	443	59	10	0	
101159	445	97	98	47	
101160	446	68	1	0	
103798	448	88	11	0	
113939	379	75	11	0	
113940	380	94	33	0	
113942	382	94	13	0	

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Inhibitors of Hypoxanthine-Guanine Phosphoribosyltransferase [1,2]

K. F. Lau and J. Frank Henderson [3]

SUMMARY

A total of 104 purine and pyrimidine derivatives and analogs were tested for their ability to inhibit hypoxanthine-guanine phosphoribosyltransferase activity in hemolysates of human erythrocytes. Three purine and nine purine nucleoside derivatives or analogs were active inhibitors under the conditions studied.

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The purine ribonucleotides which are essential for tumor growth can be synthesized de novo, from purine bases, and from purine ribonucleosides. Because such alternative metabolic pathways exist, inhibition of any one route of purine ribonucleotide synthesis cannot be expected to inhibit tumor growth completely. For this reason, screening was undertaken in this laboratory for inhibitors of purine biosynthesis de novo (1,2), adenine phosphoribosyltransferase (2,3), and adenosine kinase (2,4). In addition, we are now screening for inhibitors of hypoxanthine-guanine phosphoribosyltransferase. These comprise the major enzymes or pathways of purine ribonucleotide formation, and it is hoped that by the use of combinations of inhibitors of each important process, effective inhibition of tumor growth can be achieved. The chemotherapeutic evaluation of such compounds is now being undertaken.

Krenitsky et al (5) have determined the inhibition constants for hypoxanthine-guanine phosphoribosyltransferase of 34 compounds, 20 of which are included in this study. Kinetic studies have shown that this enzyme from human erythrocytes follows an ordered bi bi mechanism, in which PP-ribose-P binds to the enzyme before the purine base substrate (6).

The importance of hypoxanthine-guanine phosphoribosyltransferase to at least some cells has been shown in several ways. For example, an inherited deficiency of this enzyme leads to a severe neuropathy known as the Lesch-Nyhan syndrome (7), and the enzyme is believed to be involved in the supply of purines by the liver to other tissues (8) and in the re-utilization of hypoxanthine formed during ischemia (9). Thus, inhibitors of hypoxanthine-guanine phosphoribosyltransferase might have a variety of uses, as well as a variety of toxic effects.

MATERIALS AND METHODS

Unpurified preparations of hypoxanthine-guanine phosphoribosyltransferase were obtained by rapidly freezing and thawing human erythrocytes twice in a dry ice-acetone bath and dialyzing the hemolysate for 2 hours in 0.001 M Tris buffer (pH 7.4) at 4 C (10). The initial velocity of inosinate synthesis from 10 μM hypoxanthine-^{14}C (50 millicuries/mmol, Schwarz BioResearch) and 250 μM PP-ribose-P (P-L Laboratories) was measured after incubation of 100 μunits of enzyme in 100 μl of 0.1 M Tris-HCl buffer (pH 7.4) containing 5 mM $MgSO_4$ at 37 C for 5 minutes, with and without test compounds. These concentrations of substrates are equal to their Michaelis constants. Further details are given elsewhere (6). Tests were done in duplicate, and controls were run both without test compounds and without PP-ribose-P. All compounds were tested at concentrations of 1.0 mM initially; if a compound produced more than 70% inhibition, it was tested again at a lower concentration. Compounds which did not inhibit this reaction by 70% were considered inactive.

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[2] This work was supported by the National Cancer Institute of Canada.

[3] University of Alberta Cancer Research Unit (McEachern Laboratory) and Department of Biochemistry, Edmonton, Alberta, Canada.

RESULTS AND DISCUSSION

Table 1 lists the 12 compounds which inhibited hypoxanthine-guanine phosphoribosyltransferase more than 70% under the conditions used. The 92 compounds which were inactive in this assay (ie, those which inhibited the enzyme less than 70%) are listed in table 2.

Although purine was a poor inhibitor of the enzyme, the integrity of the ring itself seemed to be important in binding, since a change in the imidazole ring [ie, the *v*-triazolo(4,5-*d*)-pyrimidine and the pyrazolo(3,4-*d*)pyrimidine compounds] or a replacement of the nitrogen atoms in the ring by carbon atoms (ie, the 5,6-trimethylene pyrimidine compounds) led to decreased inhibitory activity.

Certain substitutions at the 6 position of the purine ring (ie, by amino, carboxy, cyano, methyl, or methoxy groups) decreased the inhibitory activity; however, the 6-halogen compounds produced greater inhibition, and a mercapto or hydroxylamino group at this position increased inhibitory activity a great deal.

Oxy and amino groups at the 2 position of the purine ring enhanced inhibition. Substituents at the 1, 3, 4, or 8 positions all resulted in decreased activity.

The most effective inhibitors were analogs of 6-mercaptopurine ribonucleoside in which the sugar was replaced by a tetrahydrofuran or tetrahydropyran ring. There was little inhibitory effect if the ring at the 9 position was a sugar (ie, allopyranose, arabinofuranose, ribofuranose, or xylofuranose), if the ring oxygen was replaced by sulfur (ie, thioribose), or if the ring oxygen was absent (ie, when the 9 position was linked to a cyclopentyl or phenyl group). An ethylthio group or a straight chain sugar at the 9 position of 6-mercaptopurine also abolished inhibition. Inosine and guanosine analogs with substituents on the parent purine structure all showed decreased activity. Conversion of the ribose moiety of adenosine and guanosine to hydroxymethyldiglycolaldehyde bis-phenylhydrazones produced active inhibitors.

The most active inhibitors tested by Krenitsky et al (5) were hypoxanthine, guanine, 6-mercaptopurine, and 6-thioguanine; these were also highly inhibitory in our study. 6-Chloropurine, 7-methyl-6-mercaptopurine, and 2-amino-6-methylthiopurine were slightly more active in our study than in the previous study, but in general there is agreement. Krenitsky et al did not test purine nucleosides or nucleoside derivatives and analogs, which in this study were among the most active inhibitors.

TABLE 1.—Inhibitors of hypoxanthine-guanine phosphoribosyltransferase

TABLE 1.—Inhibitors of hypoxanthine-guanine phosphoribosyltransferase

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*	Percent inhibition at concentrations of:		
						1 mM	0.1 mM	0.01 mM
755	35	6112-76-1	Purine-6-thiol, monohydrate; 6-mercaptopurine	$N_4SC_5H_4 \cdot HOH$	H	99	87	56
29570	125	10310-21-1	Purine, 2-amino-6-chloro-	$N_5ClC_5H_4$	A	82	48	
33186	258	—	9*H*-purine-6-thiol, 9-(tetrahydro-2*H*-pyran-2-yl)-	$N_4OSC_{10}H_{12}$	A	97	50	
45152	628	—	9*H*-purine, 6-iodo-9-(tetrahydro-2-furyl)-	$N_4IOC_9H_9$	A	94	57	
45153	171	—	9*H*-purine-6-thiol, 9-(tetrahydro-2-furyl)-	$N_4OSC_9H_{10}$	A	97	77	
67616	637	—	9*H*-purine-6-thiol, 9-(tetrahydro-5-methyl-2-furyl)-	$N_4OSC_{10}H_{12}$	A	98	84	37
86310	394	—	Benzenearsonic acid, *p*-[6-(2-thenylthio)-purin-8-yl]azo)-	$N_4O_3S_2AsC_{16}H_{13}$	A	88	50	
111362	345	20350-17-8	Purine-6(1*H*)-thione, 9-(2-deoxy-β-D-*erythro*-pentopyranosyl)-	$N_4O_3SC_{10}H_{12}$	F	91	58	
113547	378	16033-27-5	Purine, 2,6-bis(hydroxyamino)-	$N_6O_2C_5H_6$	A	80	42	
116931	423	—	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α'-(hydroxymethyl)-, bis(phenylhydrazone)	$N_9O_2C_{22}H_{22}$	A	74	26	
116932	424	—	Diglycolaldehyde, α-(2-amino-6-hydroxy-9*H*-purin-9-yl)-α-(hydroxymethyl)-, bis-(phenylhydrazone)	$N_9O_2C_{22}H_{22}$	A	96	52	
133418	682	—	9*H*-purine-6-thiol, 2-amino-9-D-arabinofuranosyl-, hydrate (4:1)	$N_5O_4SC_{10}H_{13} \cdot \frac{1}{4}\ HOH$	A	76	34	

*The source of each compound is coded as follows:

Code	Source	Code	Source
A	Drug Research & Development National Cancer Institute Bethesda, Md	B	Dr. A. Hampton Institute for Cancer Research 7701 Burholme Ave Fox Chase, Philadelphia, Pa

TABLE 1.—Inhibitors of hypoxanthine-guanine phosphoribosyltransferase—Continued

Code	Source
C	Dr. J. F. Henderson University of Alberta Cancer Research Unit (McEachern Laboratory) Edmonton, Alberta, Canada
D	Dr. G. A. LePage M.D. Anderson Hospital and Tumor Institute Houston, Tex
E	Dr. J. A. Montgomery Southern Research Institute Birmingham, Ala
F	Dr. R. K. Robins ICN Nucleic Acid Research Institute Irvine, Calif
G	Dr. G. M. Tener University of British Columbia Vancouver, British Columbia
H	Commercial supplier
I	Dr. H. Umezawa Institute for Microbial Chemistry Tokyo, Japan
J	Dr. B. M. Lynch St. Francis Xavier University Antigonish, Nova Scotia

TABLE 2.—Compounds inactive against hypoxanthine-guanine phosphoribosyltransferase

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*
743	11	—	Purine, 2,6-diamino-, monohydrate	$N_5C_5H_6 \cdot H_2O$	H
744	110	87-42-3	Purine, 6-chloro-	$N_4ClC_5H_3$	H
749	2	529-99-7	7*H*-*v*-triazolo[4,5-*d*]pyrimidin-7-one, 5-amino-1,6-dihydro-; 8-azaguanine	$N_6OC_4H_4$	H
753	116	120-73-0	Purine	$N_4C_5H_4$	B
756	27	552-69-2	*v*-Triazolo[4,5-*d*]pyrimidine-5,7-diol; 8-azaxanthine	$N_5O_2C_4H_3$	H
3295	281	5327-19-5	Purine, 2,6-dimethoxy-	$N_4O_2C_7H_8$	A
4910	121	—	9*H*-purine, 6-chloro-9-β-D-ribofuranosyl-	$N_4O_4ClC_{10}H_{11}$	B
4911	117	574-25-4	9*H*-purine-6-thiol, 9-β-D-ribofuranosyl-	$N_4O_4SC_{10}H_{12}$	A
5036	—	58-08-2	Caffeine	$N_4O_2C_8H_{10}$	H
7845	3	938-83-0	Guanine, 8-bromo-	$N_5OBrC_5H_4$	H
7853	39	2273-93-0	Purine, 2,6-dichloro-7-methyl-	$N_4Cl_2C_6H_4$	H
11826	6	6295-27-8	2*H*-*v*-triazolo[4,5-*d*]pyrimidin-7-ol, 5-amino-2-phenyl-	$N_6OC_{10}H_8$	A
14666	—	73-24-5	Adenine	$N_5C_5H_5$	H
15747	31	1874–58–4	Purine, 2-amino-6-(benzylthio)-	$N_5SC_{12}H_{11}$	H
15989	38	5437-25-2	Xanthine, dithio-	$N_4S_2C_5H_4$	E
17112	157	3324-79-6	Purine-6-thiol, 7-methyl-	$N_4SC_6H_6$	C
17205	52	5069-82-9	Purine, 6-(butylthio)-	$N_4SC_9H_{12}$	H
19487	59	6165-00-0	9*H*-purine-6-thiol, 9-cyclopentyl-	$N_4SC_{10}H_{12}$	H
19994	—	484-80-0	Guanosine	$N_5O_5C_{10}H_{13}$	H
20105	48	7248-15-9	Purine, 6-(methylthio)-, trihydrate	$N_4SC_6H_6 \cdot 3\ HOH$	A
20262	—	4181-51-5	Inosine	$N_4O_5C_{10}H_{12}$	H
21625	37	2036-13-7	Purine-6-carbonitrile	$N_5C_6H_3$	H
22709	28	10555-30-3	*v*-Triazolo[4,5-*d*]pyrimidin-7-ol; 8-azahypoxanthine	$N_5OC_4H_3$	H
22715	12	15986-32-0	Uric acid, 2,8-dithio-; purin-6-ol, 2,8-dimercapto-)	$N_4OS_2C_5H_4$	H
22837	—	—	Guanosine, 2'-deoxy-	$N_5O_4C_{10}H_{13}$	H
23720	24	28128-19-0	Purine-2-thiol	$N_4SC_5H_4$	H
23723	275	1074-89-1	Purine, 6-methoxy-	$N_4OC_6H_6$	H
24635	87	—	5*H*-cyclopentapyrimidin-4-ol, 2-amino-6,7-dihydro-	$N_3OC_7H_9$	A
25646	166	19769-32-5	Purine, 6-(methylsulfonyl)-	$N_4O_2SC_6H_6$	A
25803	280	—	Purine, 6-iodo-, hemihydrate	$N_4IC_5H_3 \cdot \frac{1}{2}\ H_2O$	H
26290	151	2382-18-5	9*H*-purine-6-thiol, 2-amino-9-methyl-	$N_5SC_6H_7$	F
26293	199	—	9*H*-purine-6-thiol, 9-phenyl-	$N_4SC_{11}H_8$	A

TABLE 2.—Compounds inactive against hypoxanthine-guanine phosphoribosyltransferase—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*
26294	200	5470-25-7	9*H*-purine, 6-(methylthio)-9-phenyl-	$N_4SC_{12}H_{10}$	A
28095	88	—	5*H*-cyclopentapyrimidin-4-ol, 6,7-dihydro-	$N_2OC_7H_8$	A
28111	71	—	5*H*-cyclopentapyrimidine-4-thiol, 6,7-dihydro-	$N_2SC_7H_8$	A
29420	97	1198-47-6	Purine, 2-amino-6-(methylthio)-	$N_5SC_6H_7$	A
29422	100	85-31-4	9*H*-purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-	$N_5O_4SC_{10}H_{13}$	A
29925	115	—	Inosine, 2',3'-*O*-isopropylidene-	$N_4O_5C_{13}H_{16}$	H
43405	62	16714-57-1	Purine, 6(1H)-thione, 2-amino-1-methyl-	$N_5SC_6H_7$	A
44586	119	2004-07-1	9*H*-purine, 2-amino-6-chloro-9-β-D-ribofuranosyl-	$N_5O_4ClC_{10}H_{12}$	F
45150	288	767-69-1	Purine, 6-bromo-	$N_4BrC_5H_3$	A
45762	13	13548-68-0	Xanthine, 8-chloro-	$N_4O_2ClC_5H_3$	H
46788	129	—	3*H*-*v*-triazolo[4,5-*d*]pyrimidin-7-ol, 5-amino-3-β-D-ribofuranosyl-	$N_8O_4C_9H_{13}$	E
51095	96	13020-83-2	Ammonium, trimethylpurin-6-yl-, chloride	$N_5C_8H_{12}\cdot Cl$	A
54258	158	1006-22-0	Purine-6(1*H*)-thione, 1-methyl-	$N_4SC_6H_6$	F
54461	36	—	Purine-6-carboxylic acid, hydrate	$N_4O_2C_6H_4\cdot HOH$	H
56458	228	2846-81-3	9*H*-purine, 9-(2-chloroethyl)-6-(methylthio)-	$N_4SClC_8H_9$	A
56936	229	—	9*H*-purine-6-thiol, 9-(tetrahydro-2-thienyl)-	$N_4S_2C_9H_{10}$	A
66384	147	14426-53-0	9*H*-purine, 6-iodo-9-β-D-ribofuranosyl-	$N_4O_4IC_{10}H_{11}$	A
84321	191	2946-28-3	9*H*-purine-6-thiol, 9-β-D-xylofuranosyl-	$N_4O_4SC_{10}H_{12}$	D
89804	164	—	9*H*-purine-6-thiol, 9-(5-deoxy-β-D-*ribo*-hexafuranosyl)-	$N_4O_4SC_{11}H_{14}$	D
99943	398	—	9*H*-purine-9-methanol, 6-[(4-hydroxy-2-butynyl)thio]-	$N_4O_2SC_{10}H_{10}$	A
106486	291	6743-51-7	Formycin B	$N_4O_5C_{10}H_{12}$	I
109320	372	13389-16-7	Inosine, 8-amino-	$N_5O_5C_{10}H_{13}$	A
111359	348	17434-50-3	Adenine, 9-(2-deoxy-α-D-*erythro*-pentapyranosyl)-	$N_5O_3C_{10}H_{13}$	F
111363	343	16755-05-8	Purine, 2-chloro-6-(1-piperidyl)-9-β-D-ribopyranosyl-, 2',3',4'-triacetate	$N_5O_7ClC_{21}H_{28}$	F
112511	353	19792-96-2	Adenosine, 5'-deoxy-5'-methanesulfonamido-	$N_6O_4SC_{11}H_{16}$	F
112521	361	19039-33-9	Inosine, 1,2-diamino-	$N_6O_5C_{10}H_{14}$	F
112525	365	—	Hypoxanthine, 8-bromo-	$N_4OBrC_5H_3$	F

TABLE 2.—Compounds inactive against hypoxanthine-guanine phosphoribosyltransferase—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*
112526	366	20419-68-5	9*H*-purine, 2,6-dichloro-9-(tetrahydropyran-2-yl)-	$N_4OCl_2C_{10}H_{10}$	F
112528	368	—	Adenosine, *N*-formyl-, 2',3'-diformate 5'-*p*-toluenesulfonate	$N_6O_9SC_{20}H_{19}$	F
113941	381	7697-49-6	Adenine, 9-(2-deoxy-β-D-*erythro*-pentapyranosyl)-	$N_5O_3C_{10}H_{13}$	A
113948	388	29836-04-2	Purine-6,8(1H,9H)-dione, 9-β-D-*ribo*-furanosyl-8-thio-	$N_4O_5SC_{10}H_{12}$	A
113950	390	—	Inosine, 8-methoxy-	$N_4O_6C_{11}H_{14}$	A
113987	392	—	1,2,3,4-Butanetetrol, 1,4-bis(5-chloro-2-benzimidazolyl)-, dimethanesulfonate, D-manno-	$N_4O_4Cl_2C_{18}H_{18}\cdot 2(O_3SCH_4)$	A
114860	407	28361-09-3	Adenine, 9-β-D-allopyranosyl-	$N_5O_4C_{11}H_{13}$	A
115607	417	—	Guanine, 9-β-D-xylofuranosyl-	$N_5O_5C_{10}H_{13}$	A
115963	523	—	9*H*-purine-6-thiol, 9-[D-gluco-1-(ethylthio)-2,3,4,5,6-pentahydroxyhexyl]-	$N_4O_5S_2C_{13}H_{20}$	A
118207	437	—	Hypoxanthine, 2-[(*O*-nitrobenzyl)thio]-	$N_5O_3SC_{12}H_9$	A
118209	439	—	Hypoxanthine, 8-[(*O*-nitrobenzyl)thio]-	$N_5O_3SC_{12}H_9$	A
119169	457	20789-67-7	9*H*-purine-6(1*H*)-thione, 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-	$N_4O_3SC_{11}H_{12}$	A
119664	467	—	Adenine, 9-α-D-mannofuranosyl-	$N_5O_5C_{11}H_{13}$	A
119851	474	19029-66-4	Inosine, 1-amino-	$N_5O_5C_{10}H_{13}$	A
119855	475	—	Guanosine, 5'-azido-5'-deoxy-	$N_8O_4C_{10}H_{13}$	A
119857	477	6974-67-0	Purine-6-thiol, 8-amino-	$N_5SC_5H_5$	A
125625	545	27894-31-1	Hypoxanthine, 9-β-L-fucopyranosyl-	$N_4O_5C_{11}H_{14}$	A
132067	660	27089-57-2	Guanosine, *N*-hydroxy-	$N_5O_6C_{10}H_{13}$	A
132355	665	25787-56-8	Inosine, 3'-deoxy-3'-(methylamino)-	$N_5O_4C_{11}H_{15}$	A
134681	693	—	9*H*-purine-6-thiol, 2-amino-9-(2,3-anhydro-β-D-lyxofuranosyl)-, hydrate (3:2)	$N_5O_3SC_{10}H_{11}\cdot \frac{2}{3}$ HOH	A
134682	694	—	9*H*-purine-6-thiol, 2-amino-9-β-D-xylofuranosyl-, 2'-methanesulfonate	$N_5O_6S_2C_{11}H_{15}$	A
401568	30	938-55-6	Adenine, *N*,*N*-dimethyl-	$N_5C_7H_9$	H
406021+	192	892-49-9	9*H*-purine-6-thiol, 9-β-D-arabinofuranosyl-	$N_4O_4SC_{10}H_{12}$	A
407198	46	2004-03-7	Purine, 6-methyl-	$N_4C_6H_6$	H
511952	149	—	Purine-6-thiol, 2-(methylamino)-, hemihydrate	$N_5SC_6H_7\cdot \frac{1}{2}$ HOH	F
516286+	299	5667-20-9	Adenine, *N*-hydroxy-	$N_5OC_5H_5$	H
529410+	233	—	Adenosine, *N*-hydroxy-	$N_5O_5C_{10}H_{13}$	F
—	16	—	Purine, 2-methyl-2-oxy-	$N_4OC_6H_6$	H

TABLE 2.—Compounds inactive against hypoxanthine-guanine phosphoribosyltransferase—Continued

NSC No.	CRU No.	CAS reg. No.	Compound	Molecular formula	Source*
—	17	—	Purine, 2-oxy-	$N_4OC_5H_4$	H
—	54	—	Adenine, 1-oxide	$N_5OC_5H_5$	H
—	154	—	Purine, 3-methyl-6-mercapto-	$N_4SC_6H_7$	F
—	271	—	Purine, 6-methylthio-8-hydroxy-	$N_4OSC_6H_6$	H
—	559 ML-8	—	O^6-benzylinosine	$N_4O_5C_{17}H_{18}$	C

*See footnote (*) in table 1.

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Inhibitors of Purine Metabolism in Ehrlich Ascites Tumor Cells In Vitro [1,2]

K. F. Lau and J. Frank Henderson [3]

SUMMARY

Ninety-two purine analogs and derivatives were tested for their ability to inhibit eight enzymes and two other parameters of purine metabolism in Ehrlich ascites tumor cells incubated in vitro with hypoxanthine labeled with ^{14}C. Fifty-two compounds were inhibitory in at least one system and 25 were inhibitory in two or more systems.

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Purine ribonucleotides are essential for cell growth and function, and the pathways of their synthesis and interconversion have been fruitful areas for chemotherapeutic intervention. Efforts to identify inhibitors of enzymes of purine ribonucleotide biosynthesis and metabolism have usually taken two forms. In one, individual enzymes have been assayed in the presence of potential inhibitors using cell extracts or partially purified enzymes. This approach has been very useful for determining the structural requirements for inhibitors of various enzymes, but active compounds so identified have not always been effective in intact cells. Furthermore, the enzymes studied may not be those most vital to the cells or those whose inhibition results in retarded growth.

A second approach has been to measure the effects of potential inhibitors on pathways of purine ribonucleotide metabolism or on groups of enzymes using intact cells in vivo or in vitro, usually with the aid of radioactive precursors. While this type of study is closer to the therapeutic situation, it is often difficult to determine exactly which enzyme was inhibited in the pathway measured. Therefore, the interpretation of data from structure-activity relationships becomes rather uncertain.

Because of recent developments in analytical and computational methods, we can now measure the rates of many individual enzymes of purine ribonucleotide metabolism in intact cells and simultaneously determine the effects of potential inhibitors on a number of these enzymes. In this paper we have used these methods to identify inhibitors of the following enzymes or processes in Ehrlich ascites tumor cells incubated in vitro: (*a*) hypoxanthine phosphoribosyltransferase; (*b*) adenylosuccinate synthetase plus adenylosuccinate lyase; (*c*) conversion of adenosine monophosphate (AMP) to adenosine diphosphate (ADP); (*d*) conversion of ADP to adenosine triphosphate (ATP); (*e*) inosinate (IMP) dehydrogenase; (*f*) guanosine monophosphate (GMP) synthetase; (*g*) conversion of GMP to guanosine diphosphate (GDP); and (*h*) conversion of GDP to guanosine triphosphate (GTP). In addition, we have determined the effects of potential inhibitors on the ratios ATP:ADP plus AMP and GTP:GDP plus GMP. This system has proved to be sensitive and versatile, and seems to be of considerable usefulness.

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[2] Supported by the National Cancer Institute of Canada.

[3] University of Alberta Cancer Research Unit (McEachern Laboratory) and Department of Biochemistry, Edmonton, Alberta, Canada.

MATERIALS AND METHODS

Hypoxanthine labeled at the 8 position with ^{14}C (51 millicuries/millimol, 98% pure) was purchased from Schwarz BioResearch. Purine ribonucleotides were purchased from Sigma Chemical Co., Fischer's medium from Grand Island Biological Co., and polyethyleneimine-cellulose thin-layer chromatography sheets on Mylar film from J. T. Baker Co.

Ehrlich ascites tumor cells were maintained by weekly intraperitoneal injection of 5–6 × 10^6 cells in Ha/ICR mice from our own colony or from the A. R. Schmidt Co., Madison, Wisconsin. For incubation in vitro, mice were killed and tumor cells removed and diluted at room temperature in Fischer's medium modified to contain 25 mM of phosphate buffer (pH 7.4) without bicarbonate. The cells were collected by centrifugation at room temperature and diluted in the modified Fischer's medium to make a 2.5% suspension by volume. Eighty μl of tumor cell suspension, 5 μl of medium, and 10 μl of test compounds (1 mM, final concentration) were then incubated in small plastic tubes (10 × 75 mm, Falcon Plastics) for 20 minutes at 37 C, with shaking at 120 oscillations per minute using air as the gas phase. Five μl of hypoxanthine-^{14}C was then added (0.1 mM, final concentration), and the incubation was continued. After 60 minutes, 5 μl of 4.2 M perchloric acid was added to each tube, and the cell extract was neutralized by the addition of 5 μl of 4.42 M KOH. Samples were chilled and centrifuged, and 10 μl of the supernatant was taken for chromatography studies. Purine ribonucleotides (ATP, nicotinamide adenine dinucleotide [NAD], AMP, ADP, IMP, xanthosine monophosphate [XMP], GMP, GDP, GTP), were separated by chromatography on polyethyleneimine-cellulose according to the method of Crabtree and Henderson, and the radioactivity in each compound was measured (1).

The rate of each reaction or process of purine ribonucleotide metabolism was then calculated from the amount of radioactivity which had passed through that reaction or process. Percent inhibition was calculated by comparing the rate of each reaction or process in the presence of test compound with that in control cells.

Each reaction has been corrected for any inhibition of preceding reactions which may have occurred. The mathematical basis and the computer programs used for these calculations have been published elsewhere (2). Results are averages of duplicate tests.

RESULTS AND DISCUSSION

Table A lists the 92 compounds tested in this study, and table 1 shows the percent inhibition each produced on the eight enzymes and two parameters of purine metabolism. This system is sensitive in that it detects relatively small degrees of inhibition which are difficult to measure in other ways. It is also specific in that it identifies many compounds that are inactive in all cases or are inhibitory in only one process. The usefulness and versatility of this system is indicated by its ability to identify compounds that inhibit several enzymes and to measure enzyme activities that are difficult to assay in cell extracts on a routine basis.

In some cases, measurements were also made of the incorporation of radioactive hypoxanthine into ribonucleosides and other purine bases. These compounds always constituted a relatively small percentage of the radioactivity in the metabolites of hypoxanthine, and these data did not alter the conclusions reached on the basis of measurements of ribonucleotides alone.

Although the present system seems to be satisfactory for routine screening, the computational methods are being improved so that other radioactive precursors (eg, adenine and guanine) can be used, and all metabolites and reactions can be included in the analysis. These probably would be used mainly for compounds which have shown activity in the present system.

Hypoxanthine Phosphoribosyltransferase

This enzyme was the most susceptible to inhibition of all those measured; 36 compounds

produced more than 50% inhibition, and 24 produced more than 75% inhibition. These 36 compounds are listed in table 2 in order of their inhibitory activities. Only three of the active compounds were unsubstituted at the 9 position included tetrahydrofuranose, methanribonucleosides. Other substituents at the 9 position included tetrahydrofuranose, methanol, 2′- deoxyribose, 3′- aminoribose, 4′- thioribose, and xylofuranose. Most compounds contained purine bases, but 8-azapurines, pyrazolo (4,3-*d*) pyrimidines, and pyrrolo (2,3-*d*) pyrimidines were also represented. A wide variety of substituents at the 6 position were compatible with activity, and 2-amino compounds were also active. Few were substituted in other positions.

Thirty compounds had previously been tested as inhibitors of hypoxanthine phosphoribosyltransferase using lysates of human erythrocytes and added hypoxanthine-^{14}C and PP-ribose-P (3). Of these, 12 were active in the present system and seven were less active here than when the enzyme was assayed in extracts. Six compounds were active against the enzyme but were only weakly inhibitory in the whole cell system.

Adenylosuccinate Synthetase Plus Adenylosuccinate Lyase

Only nine compounds were at all inhibitory to these enzymes, and only 21%–33% inhibition was produced (table 3). All were substituted at the 9 position with methanol, ribose, or xylose. Both 6-amino and 6-alkylthio derivatives were inhibitory, and two compounds were substituted at the 2 position. Further studies are needed to determine structural requirements for inhibition of these enzymes.

Conversion of AMP to ADP

This reaction can be catalyzed by adenylate kinase and by certain other nucleotide kinases, but the exact nature of this process under our conditions has not been determined. Eleven compounds produced more than 20% inhibition, but only one produced more than 50% inhibition (table 4). All were substituted at the 9 position with methanol or ribose. 6-Amino, 6-hydrazino, and 6-alkylthio derivatives were inhibitory.

Conversion of ADP to AMP

Active inhibitors of this process could not be identified, and the maximum inhibition observed was only 23%.

ATP:AMP Plus ADP Ratio

This ratio is an index of good energy metabolism, and 16 compounds reduced it to less than 50% of the control value; of these, 11 produced more than 75% inhibition (table 5). All were substituted at the 9 position with methanol, ribose, or other sugars, and both purine and other ring systems were compatible with activity. Most were substituted at the 6 position with amino, hydrazino, or alkylthio groups. Only a few compounds were substituted at other positions. The 11 most inhibitory compounds also inhibited at least two reactions leading from hypoxanthine to ATP, and three others also inhibited one such reaction. Two of the compounds affected this ratio without substantially affecting other processes.

Inosinate Dehydrogenase

This reaction was inhibited by 12 compounds, of which only three produced more than 50% inhibition (table 6). The inhibitory effect of mycophenolic acid is well known (4). There were a variety of substituents at the 9 and 6 positions.

Guanylate Synthetase

The active inhibitors of this reaction could not be identified, and the maximum inhibition produced was 22%.

Conversion of GMP to GDP

No active inhibitors of this process were identified, and the maximum inhibition produced was 31%.

Conversion of GDP to GTP

Eleven compounds inhibited this reaction significantly, although only two produced more than 50% inhibition (table 7). There were a variety of substituents at the 6 and 9 positions, and several substituents at the 2 position.

GTP:GDP Plus GMP Ratio

Fifteen compounds reduced this ratio to 50% of the control value or less, and three produced more than 75% inhibition (table 8). Three, including mycophenolic acid, are not nucleosides and are not otherwise substituted at the 9 position. A variety of substituents are permitted at this position, however, as well as at the 6 position.

Inhibition of Two or More Reactions

Of the 52 different compounds listed in tables 2–8, three inhibited five systems, nine inhibited four, six inhibited three, and seven inhibited two. These inhibitors of multiple processes are listed in table 9. Seventeen compounds inhibited only hypoxanthine phosphoribosyltransferase, six inhibited only inosinate dehydrogenase, two inhibited only the GTP:GMP plus GDP ratio, and one inhibited only the ATP:AMP plus ADP ratio.

TABLE A.—List of compounds tested

NSC No.	CRU No.	Compound	Molecular formula	Source	CAS registry No.
755	35	Purine-6-thiol-, monohydrate; 6-mercaptopurine	$N_4SC_5H_4 \cdot H_2OH$	H	6112-76-1
3056	132	Adenosine, 3'-amino-3'-deoxy-*N*,*N*-dimethyl-	$N_6O_3C_{12}H_{18}$	A	—
4910	121	9*H*-purine, 6-chloro-9-β-D-ribofuranosyl-	$N_4O_4ClC_{10}H_{11}$	B	—
4911	117	9*H*-purine-6-thiol, 9-β-D-ribofuranosyl-	$N_4O_4SC_{10}H_{12}$	A	574-25-4
7359	190	Adenine, 9-β-D-xylofuranosyl-	$N_5O_4C_{10}H_{13}$	D	—
7363	128	9*H*-purine, 2,6-diamino-9-β-D-ribofuranosyl-	$N_6O_4C_{10}H_{14}$	B	2096-10-8
11641	375	1*H*-pyrazolo[3,4-*d*]pyrimidine, 4-phenethylamino-, hydrochloride	$N_5C_{13}H_{13} \cdot HCl$	A	—
12161	175	Isoguanosine	$N_5O_5C_{10}H_{13}$	A	—
14576	197	9*H*-purine, 9-ethyl-6-(methylthio)-	$N_4SC_8H_{10}$	A	7252-00-8
18192	89	Adenosine, 3'-amino-3'-deoxy-	$N_6O_3C_{10}H_{14}$	A	2504-55-4
22744	279	Adenine, 8-methyl-	$N_5C_6H_7$	A	22387-37-7
26294	200	9*H*-purine, 6-(methylthio)-9-phenyl-	$N_4SC_{12}H_{10}$	A	5470-25-7
29408	292	9*H*-purine, 6-hydrazino-9-β-D-ribofuranosyl-	$N_6O_4C_{10}H_{14}$	E	25840-47-5
29409	136	Adenosine, *N*-methyl-	$N_6O_4C_{11}H_{15}$	H	—
29422	100	9*H*-purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-	$N_5O_4SC_{10}H_{13}$	A	85-31-4
29570	125	Purine, 2-amino-6-chloro-	$N_5ClC_5H_4$	A	10310-21-1
30605	131	Adenosine, 2-fluoro-	$N_5O_4FC_{10}H_{12}$	A	146-78-1
30606	126	9*H*-purine, 6-methoxy-9-β-D-ribofuranosyl-	$N_4O_5C_{11}H_{14}$	F	5746-29-2
33186	258	9*H*-purine-6-thiol, 9-(tetrahydro-2*H*-pyran-2-yl)-	$N_4OSC_{10}H_{12}$	A	—
33686	172	Adenine, 9-β-D-glucofuranosyl-	$N_5O_5C_{11}H_{15}$	A	6273-05-8
39368	183	9*H*-purine, 6-(ethylthio)-9-β-D-ribofuranosyl-, monohydrate	$N_4O_4SC_{12}H_{16} \cdot HOH$	A	—
45152	628	9*H*-purine, 6-iodo-9-(tetrahydro-2-furyl)-	$N_4OIC_9H_9$	A	—
45153	171	9*H*-purine-6-thiol, 9-(tetrahydro-2-furyl)-	$N_4OSC_9H_{10}$	A	—
51470	307	Acetic acid, (2-amino-9-propyl-9*H*-purin-6-ylthio)-	$N_5O_2SC_{10}H_{13}$	A	—
54251	148	Adenosine, *N*-(2-hydroxyethyl)-, monohydrate	$N_6O_5C_{12}H_{17} \cdot HOH$	A	—
56408	103	7*H*-pyrrolo[2,3-*d*]pyrimidine, 4-amino-7-β-D-ribofuranosyl-; tubercidin	$N_4O_4C_{11}H_{14}$	A	69-33-0
65423	130	9*H*-purine, 9-β-D-ribofuranosyl-	$N_4O_4C_{10}H_{12}$	B	—
66381	124	9*H*-purine, 2-amino-6-methoxy-9-β-D-ribofuranosyl-	$N_5O_5C_{11}H_{15}$	F	7803-88-5
66384	147	9*H*-purine, 6-iodo-9-β-D-ribofuranosyl-	$N_4O_4IC_{10}H_{11}$	A	14426-53-0

TABLE A.—List of compounds tested—Continued

NSC No.	CRU No.	Compound	Molecular formula	Source	CAS registry No.
67616	637	9*H*-purine-6-thiol, 9-(tetrahydro-5-methyl-2-furyl)-	$N_4OSC_{10}H_{12}$	A	—
70423	558 (ML7)	Adenosine, *N*-benzyl-	$N_5O_4C_{17}H_{19}$	B	4294-16-0
	559 (ML8)	O^4-benzylinosine	$N_4O_5C_{17}H_{18}$	B	—
	160	Decoyinine	$N_5O_4C_{12}H_{13}$	C	—
72961	127	3*H*-*v*-triazolo[4,5-*d*]pyrimidine, 7-amino-3-β-D-ribofuranosyl-	$N_6O_4C_9H_{12}$	A	10299-44-2
79213	247	Adenosine, 8-bromo-	$N_5O_4BrC_{10}H_{12}$	F	2946-39-6
82219	186	Adenosine, 4'-thio-	$N_5O_3SC_{10}H_{13}$	D	2500-80-3
82223	194	Adenine, 9-(5-deoxy-β-D-ribohexofuranosyl)-	$N_5O_4C_{11}H_{13}$	D	2946-34-1
84321	191	9*H*-purine-6-thiol, 9-β-D-xylofuranosyl-	$N_4O_4SC_{10}H_{12}$	D	2946-28-3
86310	394	Benzenearsonic acid, *p*-([6-(2-thenylthio)-purin-8-yl]-azo)-	$N_6O_5S_2AsC_{16}H_{13}$	A	—
87676	163	Adenine, 9-β-L-ribofuranosyl-	$N_5O_4C_{10}H_{13}$	D	3080-29-3
90397	240	Adenosine, 8-methoxy-	$N_5O_5C_{11}H_{15}$	F	3969-27-5
91041	188	Adenine, 9-β-D-lyxofuranosyl-	$N_5O_4C_{10}H_{13}$	D	4005-33-8
95103	195	9*H*-purine, 6-(methylthio)-9-β-D-xylofuranosyl-	$N_4O_4SC_{11}H_{14}$	D	15397-51-0
98671	339	Adenine, 9-(3-amino-3-deoxy-β-D-arabinofuranosyl)-	$N_6O_3C_{10}H_{14}$	A	26315-51-5
99935	397	9*H*-purine-9-methanol, 6-(cyclopentylthio)-	$N_4OSC_{11}H_{14}$	A	14196-96-4
100279	444	7*H*-pyrrolo[2,3-*d*]pyrimidine, 4-(dimethylamino)-7-β-D-ribofuranosyl-	$N_4O_4C_{13}H_{19}$	F	20371-00-0
102811	290	Formycin	$N_5O_4C_{10}H_{13}$	I	6742-12-7
105546	422	Adenosine, *N*-(3-methyl-2-butenyl)-	$N_5O_4C_{15}H_{21}$	A	7724-76-7
109320	372	Inosine, 8-amino-	$N_5O_5C_{10}H_{13}$	A	13389-16-7
111356	351	Purine-6(1*H*)-thione, 7-β-D-ribofuranosyl-	$N_4O_4SC_{10}H_{12}$	F	20187-89-7
111358	349	Benzimidazole, 2-chloro-	$N_2ClC_7H_5$	F	4857-06-1
111359	348	Adenine, 9-(2-deoxy-α-D-*erythro*-pentopyranosyl)-	$N_5O_3C_{10}H_{13}$	F	17434-50-3
111360	347	Pyrrolo[2,3-*d*]pyrimidine, 4-hydrazino-7-β-D-ribofuranosyl-	$N_5O_4C_{11}H_{15}$	F	—
111362	345	Purine-6(1*H*)-thione, 9-(2-deoxy-β-D-*erythro*-pentopyranosyl)-	$N_4O_3SC_{10}H_{12}$	F	20350-17-8
112511	353	Adenosine, 5'-deoxy-5'-methanesulfonamido-	$N_6O_5SC_{11}H_{16}$	F	19792-96-2
112515	357	Glucopyranoside, 6-aminopurin-8-yl-1-thio-, β-D-	$N_5O_5CS_{11}H_{15}$	F	25253-77-4
112526	366	9*H*-purine, 2,6-dichloro-9-(tetrahydropyran-2-yl)-	$N_4OCl_2C_{10}H_{10}$	F	20419-68-5

TABLE A.—List of compounds tested—Continued

NSC No.	CRU No.	Compound	Molecular formula	Source	CAS registry No.
112742	369	2-Benzimidazolethiol, 1-[2-(4-pyridyl)-ethyl]-	$N_3SC_{14}H_{13}$	F	13083-37-9
113547	378	Purine, 2,6-bis(hydroxyamino)-	$N_6O_2C_5H_6$	A	16033-27-5
113939	379	7*H*-pyrrolo[2,3-*d*]pyrimidine, 4-amino-5-iodo-7-β-D-ribofuranosyl-	$N_4O_4IC_{11}H_{12}$	A	24386-93-4
113940	380	7*H*-pyrrolo[2,3-*d*]pyrimidine, 4-chloro-5-iodo-7-β-D-ribofuranosyl-	$N_3O_4ClIC_{11}H_{11}$	A	24386-91-2
113942	382	7*H*-pyrrolo[2,3-*d*]pyrimidine, 5-bromo-4-(methylthio)-7-β-D-ribofuranosyl-	$N_3O_4SBrC_{12}H_{14}$	A	24386-90-1
113949	389	Inosine, 8-(methylthio)-	$N_4O_5SC_{11}H_{14}$	A	2104-65-6
114334	401	9*H*-purine-9-methanol, 6-(butylthio)-	$N_4OSC_{10}H_{14}$	A	14196-95-3
114337	404	9*H*-purine-9-methanol, 8-methyl-6-(propylthio)-	$N_4OSC_{10}H_{14}$	A	—
114754	405	Theobromine, 8-(chloromethyl)-	$N_4O_2ClC_8H_9$	A	4921-56-6
114755	406	Theobromine, 8-(hydroxymethyl)-	$N_4O_3C_8H_{10}$	A	—
114861	408	Adenine, 9-α-D-talopyranosyl-	$N_5O_5C_{11}H_{13}$	A	—
116931	423	Diglycolaldehyde, α-(6-amino-9*H*-purin-9-yl)-α-(hydroxymethyl)-, bis(phenylhydrazone)	$N_9O_2C_{22}H_{22}$	A	—
116932	424	Diglycolaldehyde, α-(2-amino-6-hydroxy-9*H*-purin-9-yl)-α-(hydroxymethyl)-, bis(phenylhydrazone)	$N_9O_3C_{22}H_{22}$	A	—
117835	427	1*H*-pyrazolo[3,4-*d*]pyrimidine-3-carbonitrile, 4-amino-1-methyl-	$N_6C_7H_6$	A	—
117839	431	7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile, 4-chloro-7-β-D-ribofuranosyl-	$N_4O_4ClC_{12}H_{11}$	A	—
117841	432	Xanthosine, 8-amino-	$N_5O_6C_{10}H_{13}$	A	13389-08-7
117843	434	9*H*-purine, 2-amino-8-chloro-6-(dimethylamino)-9-β-D-ribofuranosyl-	$N_6O_4ClC_{12}H_{17}$	A	15717-47-2
117844	435	9*H*-purine, 2-amino-8-chloro-6-piperidino-9-β-D-ribofuranosyl-	$N_6O_4ClC_{15}H_{21}$	A	15717-48-3
119169	457	9-*H*-purine-6(1*H*)-thione, 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-	$N_4O_3SC_{11}H_{12}$	A	20789-67-7
119662	465	Adenine, 9-β-D-gulofuranosyl-	$N_5O_5C_{11}H_{13}$	A	10279-87-5
119843	468	Adenosine, 5′-azido-2′-5′-dideoxy-	$N_8O_3C_{10}H_{12}$	A	—
119847	471	Guanosine, 8-(benzyloxy)-1-methyl-	$N_5O_6C_{18}H_{21}$	A	27963-76-4
119855	475	Guanosine, 5′-azido-5′-deoxy-	$N_8O_4C_{10}H_{12}$	A	—
119857	477	Purine-6-thiol, 8-amino-	$N_5SC_5H_5$	A	6974-67-0
129185		4-Hexenoic acid, 6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-, (*E*)-; mycophenolic acid	$C_{17}H_{20}O_6$		—

TABLE A.—List of compounds tested—Continued

NSC No.	CRU No.	Compound	Molecular formula	Source	CAS registry No.
141848	794	Adenosine, 21-deoxy-, monohydrate	$N_5O_3C_{10}H_{13}\cdot HOH$	A	16373-93-6
142996	795	Adenine, 9-(4-*C*-cyclopropyl-β-D-*xylo*-tetrofuranosyl)-	$N_5O_4C_{12}H_{15}$	A	33585-52-3
143510	—	Adenosine, 2'-deoxy-, monohydrate	$N_5O_3C_{10}H_{13}\cdot HOH$	H	16373-93-6
143682	796	1*H*-imidazo[4,5-*b*]pyrazine, 1-β-D-ribofuranosyl-	$N_4O_4C_{10}H_{12}$	A	—
143684	797	2*H*-pyrazolo[4,3-*d*]pyrimidine, 7-amino-2-methyl-3-β-D-ribofuranosyl-	$N_5O_4C_{11}H_{13}$	A	—
143686	798	Formamidine, *N'*-(5-cyano-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-*N*,*N*-dimethyl-	$N_6O_4C_{13}H_{15}$	A	—
143687	799	7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide, 7-β-D-ribofuranosylthio-, hemihydrate	$N_4O_4SC_{12}H_{14}\cdot \frac{1}{2}HOH$	A	—
404241	153	Adenine, 9-β-D-arabinofuranosyl-	$N_5O_4C_{10}H_{13}$	D	5536-17-4
529410+	233	Adenosine, *N*-hydroxy-	$N_5O_5C_{10}H_{13}$	F	—
—	—	Coformycin	—	—	—

*The source of each compound is coded as follows:

Code	Source
A	Drug Research & Development National Cancer Institute Bethesda, Md
B	Dr. A. Hampton Institute for Cancer Research 7701 Burholme Ave Fox Chase, Philadelphia, Pa
C	Dr. J. F. Henderson University of Alberta Cancer Research Unit (McEachern Laboratory) Edmonton, Alberta, Canada
D	Dr. G. A. LePage M. D. Anderson Hospital and Tumor Institute Houston, Tex
E	Dr. J. A. Montgomery Southern Research Institute Birmingham, Ala
F	Dr. R. K. Robins ICN Nucleic Acid Research Institute Irvine, Calif
G	Dr. G. M. Tener University of British Columbia Vancouver, British Columbia
H	Commercial supplier
I	Dr. H. Umezawa Institute for Microbial Chemistry Tokyo, Japan
J	Dr. B. M. Lynch St. Francis Xavier University Antigonish, Nova Scotia

TABLE 1.—Inhibitors of purine metabolism in Ehrlich ascites tumor cells

NSC No.	CRU No.	Total nucleotides	Adenine nucleotide synthesis				Guanine nucleotide synthesis				
		H → IMP	IMP → AMP	AMP → ADP	ADP → ATP	ATP: AMP + ADP	IMP → XMP	XMP → GMP	GMP → GDP	GDP → GTP	GTP: GMP + GDP
			Percent Inhibition								
755	35	61.8	3.6	2.1	−0.5	12.5	−2.4	5.2	0.0	6.5	24.2
3056	132	−1.9	−1.3	−1.2	−1.5	−1.4	−1.5	−0.5	−0.1	4.2	17.7
4910	121	72.6	16.7	0	0.88	14.5	−68.9	2.16	−2.2	64.1	72.4
4911	117	62.1	6.33	2.69	0.29	20.1	3.17	4.63	2.86	12.3	30.4
7359	190	90.4	20.8	10.7	−3.1	79.3	−71.8	17.5	8.09	33.6	50.0
7363	128	93.2	17.1	28.0	−2.4	85.4	−48.5	11.8	13.4	19.4	40.1
11641	375	47.0	6.23	4.63	8.02	48.9	−25.1	7.39	6.68	−1.2	−1.1
12161	175	77.5	23.5	2.91	1.20	39.6	−159.0	−0.3	0	−7.8	−1.5
14576	197	−0.5	−4.76	−1.3	−1.0	−1.9	17.7	0.58	1.75	−1.3	−1.2
18192	89	70.6	4.42	−1.8	−5.6	−1.2	−18.3	8.55	0.1	−1.3	−1.2
22744	279	2.0	−1.4	−3.0	−6.6	−1.3	9.90	−7.4	−6.0	−1.2	−1.4
26294	200	12.7	−6.9	−0.7	−1.6	−1.3	9.05	−8.4	−0.2	−6.0	−1.2
29408	292	88.8	27.6	37.0	11.7	87.5	−75.8	16.7	21.3	−5.4	28.3
29409	136	76.7	6.87	2.86	3.79	31.5	−8.5	12.6	4.98	−1.4	−1.1
29422	100	85.1	8.05	4.38	−0.7	30.1	−3.4	−1.3	2.56	−2.6	0.0
29570	125	52.1	−1.1	2.08	−6.9	−1.2	45.9	10.8	2.60	24.0	46.9
30605	131	94.1	30.5	46.3	22.7	95.6	−61.1	16.8	25.3	−10.2	24.8
30606	126	86.7	13.5	2.61	0.89	23.6	−6.7	9.86	12.5	−1.6	−1.7
33186	258	25.0	3.33	4.69	−0.4	16.1	−16.3	0	1.26	2.32	8.5
33686	172	14.4	1.64	−0.7	−1.5	−1.2	−8.1	0.76	2.29	2.23	19.4
39368	183	−1.3	4.03	20.4	−1.6	52.5	−22.2	−0.8	−3.6	46.0	54.4
45152	628	72.4	1.09	−4.7	−4.9	−1.3	4.71	−2.6	−7.0	−11.6	−1.4
45153	171	72.3	−0.4	9.71	3.59	42.8	−8.3	8.67	1.46	8.15	20.9
51470	307	−0.7	1.49	2.17	0.87	14.2	−26.0	20.2	0.28	0.17	8.4
54251	148	7.7	−2.1	−2.1	−1.0	−1.2	18.4	−0.4	1.59	−19.4	−1.4
56408	103	91.2	21.5	42.0	10.0	93.4	−51.1	12.0	15.3	−24.2	−1.1
65423	130	91.9	23.4	38.7	0	91.3	−22.2	16.1	31.3	−31.5	14.0
66381	124	81.1	1.59	1.08	0.54	17.4	66.6	17.4	9.62	48.9	85.9
66384	147	24.3	19.6	−1.1	1.46	3.1	−90.6	2.22	−2.7	86.5	90.4
67616	637	85.6	5.56	1.47	0	17.8	8.33	6.06	−0.8	8.00	26.2
72961	127	84.4	15.38	6.06	−5.6	21.4	−66.7	−4.2	27.31	−7.6	32.3
72913	247	−1.2	−10.5	2.57	1.10	11.8	46.7	−6.2	−1.4	−9.3	−1.3
82223	194	45.1	−6.4	0	−0.1	8.2	19.0	5.11	9.13	−24.5	−1.3
84321	191	−1.0	3.22	−0.17	−1.4	−1.3	−29.8	−0.1	−1.1	30.6	68.5
86310	394	46.3	2.61	0.57	5.38	23.4	−32.6	−3.5	−8.9	24.1	34.8
87676	163	−1.4	−9.1	−1.8	−2.8	−1.5	7.72	−5.8	−11.0	−0.6	−1.6
90397	240	−1.1	−3.7	−2.0	−1.5	−1.3	26.1	2.72	3.27	−37.1	28.3
91041	188	4.8	1.05	−0.5	0.32	−1.0	−6.7	0	0.1	−1.4	−1.1
95103	195	−1.1	−5.5	0.84	−0.8	−1.0	−6.4	−5.9	−9.1	−12.3	−1.5
98671	339	−1.3	−0.6	3.41	−1.6	8.0	5.00	2.28	2.33	−0.2	7.9
99935	397	93.2	30.8	55.3	23.8	97.4	−77.9	19.0	29.5	30.4	80.8
100279	444	56.0	5.68	3.86	1.25	28.2	−13.6	22.6	8.01	−28.9	−1.5
105546	422	64.8	3.41	1.76	3.24	19.4	−6.5	8.80	4.39	27.5	49.7
109320	372	59.7	2.48	1.27	−1.0	5.9	−21.6	10.2	3.41	−11.5	−1.2
111356	351	−1.0	2.79	2.25	2.51	23.4	−2.8	0.39	1.36	11.4	37.1
111358	349	5.0	0.11	−2.0	8.57	33.7	−15.4	8.20	0.79	10.4	21.9
111359	348	15.8	6.06	0.13	−1.0	−1.1	−51.7	−0.5	−2.2	26.9	43.1
111360	347	87.7	27.6	37.0	8.93	88.7	−75.6	22.6	21.5	−3.8	33.8
111362	345	48.5	0.57	0.58	−1.2	−1.1	15.3	2.06	−2.3	6.41	16.1
112511	353	4.1	−2.1	−1.4	−1.6	−1.2	−6.6	0.68	−1.2	−2.5	−1.1
112515	357	6.3	−2.0	0.10	0.94	9.7	−1.7	0.42	0.42	9.52	35.9
112526	366	49.8	−5.6	1.70	4.03	41.4	38.4	−0.35	0.96	30.8	53.9
112742	369	0.7	0.81	−1.0	−1.9	−1.2	−26.0	4.39	−2.4	10.2	16.5
113547	378	35.7	0.16	2.18	−1.9	2.2	34.0	3.51	−0.7	8.67	18.2
113939	379	−1.0	−4.5	−1.4	1.06	−1.0	−3.2	−0.8	−1.9	22.7	37.7

TABLE 1.—Inhibitors of purine metabolism in Ehrlich ascites tumor cells—Continued

NSC No.	CRU No.	Total nucleotides	Adenine nucleotide synthesis				Guanine nucleotide synthesis				
		H → IMP	IMP → AMP	AMP → ADP	ADP → ATP	ATP: AMP + ADP	IMP → XMP	XMP → GMP	GMP → GDP	GDP → GTP	GTP: GMP + GDP
			Percent Inhibition								
113940	380	50.8	−1.6	5.20	16.0	65.2	−10.7	3.49	8.37	47.1	70.4
113942	382	1.5	−9.1	0.19	1.96	11.9	25.9	1.78	2.51	−0.4	4.6
113949	389	−1.1	4.23	10.4	3.70	54.3	1.24	6.43	6.59	7.36	38.7
114334	401	90.6	32.9	33.3	14.2	95.1	−74.4	21.3	24.0	9.18	49.6
114337	404	89.3	28.9	35.5	16.3	94.9	−79.4	22.4	28.1	4.67	50.8
114754	405	19.2	−2.8	1.27	−0.6	3.6	−5.7	5.62	0.87	−2.0	−1.0
114755	406	−1.1	1.39	9.43	1.85	47.9	2.87	6.18	11.5	7.02	46.7
114861	408	−1.0	4.00	13.1	4.45	60.1	−15.2	6.10	9.75	21.0	62.0
116931	423	92.1	25.3	37.3	5.41	89.4	−130.0	9.89	14.4	20.0	52.2
116932	424	76.2	−1.6	1.34	0	15.4	60.1	14.4	9.86	50.0	85.0
117835	427	−1.1	−9.2	−7.2	−0.5	−1.5	−5.3	−1.3	−8.3	18.6	21.1
117839	431	27.6	−6.4	0.39	4.56	25.3	26.3	4.16	5.84	56.9	76.7
117841	432	−0.51	1.81	8.91	3.40	51.7	8.37	3.84	6.48	4.85	34.1
117843	434	16.9	−1.8	−0.3	−2.0	−29.9	12.6	2.34	2.68	−8.7	−28.5
117844	435	4.00	−0.5	−0.1	−0.3	−0.9	14.1	0.24	0.49	−3.0	−11.5
119169	457	10.2	4.45	6.15	0.72	34.1	5.79	4.73	8.06	−1.6	22.0
119662	465	−14.6	−0.4	6.43	−1.3	25.2	10.9	3.33	9.13	−7.2	9.60
119843	468	5.50	4.49	7.02	0.24	35.6	−20.5	2.11	5.65	21.4	58.6
119847	471	−15.3	1.30	9.49	0.29	42.5	4.51	2.72	7.94	5.48	37.6
119855	475	43.6	−6.6	0.17	0.33	4.9	24.6	22.8	5.79	33.6	57.5
119857	477	−0.7	4.75	1.27	0.89	10.8	−64.5	8.95	−5.4	37.0	50.0
141848	794	87.2	9.37	7.76	0	51.3	−34.4	−3.5	3.37	2.33	12.5
142996	795	1.7	−11.9	−2.1	−3.9	−76.8	29.7	−2.8	−9.7	5.70	−13.6
143682	796	1.2	−5.7	0.77	−2.6	−19.1	−1.5	1.79	0.20	−1.3	−0.4
143684	797	−35.8	−10.6	−3.4	−3.3	−93.7	4.38	−6.6	−10.6	−4.8	−94.4
143686	798	7.4	−10.0	−2.3	−3.8	−81.0	25.9	−3.0	−7.3	−0.2	−37.7
143687	799	5.5	−8.0	0	−0.7	−0.9	−11.8	−5.4	1.85	19.4	38.6
404241	153	8.5	0.45	−2.4	−1.1	−23.2	−3.9	0.73	1.49	−2.0	−0.3
529410+	233	96.0	32.5	7.41	0	58.1	−11.2	8.89	9.76	−18.9	−21.1
82219	186	88.3	11.1	5.77	−6.1	29.4	−28.2	10.6	9.96	−27.1	−25.8
70423	558 (ML7)	45.8	1.48	2.06	0.96	15.1	15.6	5.47	7.17	15.4	52.5
—	559 (ML8)	62.6	3.74	4.72	1.75	33.6	−9.9	10.5	2.19	−4.7	−10.8
—	160	47.8	8.05	2.71	−6.0	−10.1	−34.2	1.43	1.88	−5.1	−0.5
102811	290	80.5	14.3	19.7	5.97	67.6	−25.6	8.16	7.11	−69.8	−225.0
143510 *	—	77.1	13.5	4.04	−2.1	15.4	−55.5	5.62	5.06	28.9	41.0
129185	—	8.4	2.29	−0.1	0.45	2.5	−13.7	0.76	2.90	6.57	34.3
		−0.6	−6.8	−1.9	−0.3	−22.6	87.7	14.6	8.21	47.5	79.1

*Coformycin.

TABLE 2.—Inhibitors of hypoxanthine phosphoribosyltransferase

NSC No.	CRU No.	Percent inhibition
529410	233	96.0
30605	131	94.1
99935	397	93.2
7363	128	93.2
116931	423	92.1
65423	130	91.9
56408	103	91.2
114334	401	90.6
7359	190	90.4
114337	404	89.3
29408	292	88.8
82219	186	88.3
111360	347	87.7
141848	794	87.2
30606	126	86.7
67616	637	85.6
29422	100	85.1
72961	127	84.4
66381	124	81.1
102811	290	80.5
12161	175	77.5
143510	—	77.1
29409	136	76.7
116932	424	76.2
45152	628	72.4
45153	171	72.3
18192	89	70.6
4910	121	72.6
105546	422	64.8
—	559	62.6
4911	117	62.1
755E	35	61.8
109320	372	59.7
100279	444	56.0
29570	125	52.1
113940	380	50.8

TABLE 3.—Inhibition of adenylosuccinate synthetase and adenylosuccinate lyase

NSC No.	CRU No.	Percent inhibition
114334	401	32.9
99935	397	30.8
30605	131	30.5
114337	404	28.9
111360	347	27.6
29408	292	27.6
116931	423	25.3
12161	175	23.5
7359	190	20.8

TABLE 4.—Inhibition of the conversion of AMP to ADP

NSC No.	CRU No.	Percent inhibition
99935	397	55.3
30605	131	46.3
56408	103	42.0
65423	130	38.7
116931	423	37.3
29408	292	37.0
111360	347	37.0
114337	404	35.5
114334	401	33.3
7363	128	28.0
39368	183	20.4

TABLE 5.—Inhibition of the ATP:AMP + ADP ratio

NSC No.	CRU No.	Percent inhibition
99935	397	97.4
30605	131	95.6
114334	401	95.1
114337	404	94.9
56408	103	93.4
65423	130	91.3
116931	423	89.4
29408	292	87.5
7363	128	85.4
111360	347	88.7
7359	190	79.3
102811	290	67.6
113940	380	65.2
114861	408	60.1
39368	183	52.5
117841	432	51.7

TABLE 6.—Inhibitors of inosinate dehydrogenase

NSC No.	CRU No.	Percent inhibition
129185	—	87.7
66381	124	66.6
116932	424	60.1
29570	125	45.9
112526	366	38.4
113547	378	34.0
142996	795	29.7
90397	240	26.1
143686	798	25.9
113942	382	25.9
117839	431	26.3
119855	475	24.6

TABLE 7.—Inhibitors of the conversion of GDP to GTP

NSC No.	CRU No.	Percent inhibition
117839	431	56.9
116932	424	50.0
66381	124	48.9
129185	—	47.5
113940	380	47.1
39368	183	46.0
119857	477	37.0
7359	190	33.6
119855	475	33.6
84321	191	30.6
99935	397	30.4

TABLE 8.—Inhibitors of the GTP:GDP + GMP ratio

NSC No.	CRU No.	Percent inhibition
66381	124	85.9
116932	424	85.0
129185	—	79.1
117839	431	76.7
4910	121	72.4
113940	380	70.4
84321	191	68.5
114861	408	62.0
119843	468	58.6
119855	475	57.5
39368	183	54.4
70423	558	52.5
114337	404	50.8
7359	190	50.0
119857	477	50.0

TABLE 9.—Inhibitors of two or more enzymes

NSC No.	CRU No.	Enzyme or process inhibited (from tables 2–8)									
		Total nucleotides	Adenine nucleotide synthesis				Guanine nucleotide synthesis				
		H → IMP	IMP → AMP	AMP → ADP	ADP → ATP	ATP: AMP + ADP	IMP → XMP	XMP → GMP	GMP → GDP	GDP → GTP	GTP: GMP + GDP
114337	404	+	+	+		+					+
99935	397	+	+	+		+				+	
7359	190	+	+			+				+	+
66381	124	+					+			+	+
116931	423	+	+	+		+					
116932	424	+					+			+	+
30605	131	+	+	+		+					
114334	401	+	+	+		+					
113940	380	+				+				+	+
29408	292	+	+	+		+					
111360	347	+	+	+		+					
39368	183			+		+				+	+
7363	128	+		+		+					
65423	130	+		+		+					
56408	103	+		+		+					
129185	—						+			+	+
119855	475						+			+	+
117839	431						+			+	+
114861	408					+					+
12161	175	+	+								
4910	121	+									+
29570	125	+					+				
119857	477									+	+
84321	191									+	+
102811	290	+				+					

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The Influence of Schedule of Administration of Mitomycin C (NSC-26980) in the Treatment of L1210 Leukemia [1]

R. Kojima,[2] A. Goldin,[3] and N. Mantel [4]

SUMMARY

Studies have been conducted on the schedule dependency of mitomycin C in the treatment of mice with L1210 leukemia. On standard schedules of administration, there is only limited schedule dependency. Mitomycin C was about equally effective in increasing survival time of leukemic mice on a daily or every-2-, every-3-, or every-4-day schedule. However, on a treatment schedule of every 7 or every 8 days, there was a definite reduction in therapeutic effectiveness. Schedule dependency became more manifest on further alteration of scheduling. With a priming dose of mitomycin C, which appears to lower leukemic cell population, followed by an intermittent schedule of therapy with low doses of the drug, improved therapeutic efficacy was noted. The subsequent reduction in dose and the use of an intermittent schedule may in turn permit preferential recovery of the host. The studies suggest that the degree of schedule dependency of a drug may be manipulated by taking into account factors pertaining to the tumor and the host which may limit drug effectiveness.

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The mitomycins are a group of substances isolated from fermentation filtrates of *Streptomyces caespitosus*. Mitomycin A and B were isolated by Hata et al (1), and a series of additional fractions including mitomycin C were isolated from an improved strain by Wakaki et al (2).[5]

Mitomycin C has demonstrated activity against a wide spectrum of animal tumors (3,4). It has been employed extensively in Japan to treat neoplasia (5), and has been in clinical trial in the United States since 1959 (6). Clinically, it has been shown active against chronic myelogenous leukemia, a variety of tumors (including those of the colon, breast, lung, stomach, pancreas, liver, and head and neck), osteogenic sarcoma, Hodgkin's disease, lymphoma, and rhabdomyosarcoma (5,6). However, its use has been severely limited by its toxic action, including severe bone marrow depression and gastrointestinal damage (7).

Since it has been demonstrated that clin-

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[2] Kyowa Hakko Kogyo Company, Ltd., Tokyo, Japan. Work performed while guest worker in Division of Cancer Treatment (DCT), National Cancer Institute (NCI), Bethesda, Md.

[3] Drug Research and Development, DCT, NCI, Bethesda, Md.

[4] Biometry Branch, NCI, Bethesda, Md.

[5] Mitomycin A: NSC-75986; CAS reg. No. 4055-39-4; (azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 1,1*a*,-2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-6,8*a*-dimethoxy-5-methyl-, carbamate).

Mitomycin B: NSC-75987; CAS reg. No. 4055-40-7; (azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 1,1*a*,-2,8,8*a*,8*b*-hexahydro-8*a*-hydroxy-8-(hydroxymethyl)-6-methoxy-1,5-dimethyl-, 8-carbamate).

Mitomycin C: NSC-26980; CAS reg. No. 50-07-7; azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbamate (ester).

ically active drugs may be schedule-dependent (8–13), we felt it important to determine the schedule-dependency characteristics of mitomycin C.

MATERIALS AND METHODS

L1210 leukemia was carried in DBA/2 mice, and for the experiments was implanted intraperitoneally (ip) (10^5 cells) into CDF_1 hybrid male (BALB/c female × DBA/2 male) mice. Unless otherwise noted, each group (treated and control) contained five mice. Mitomycin C was obtained from Bristol Laboratories and the Kyowa Hakko Kogyo Co., Ltd. The drug was prepared in saline and injected at 0.01 ml/g of body weight. It was administered ip starting 1 day after leukemic inoculation. The dosage schedules for the individual experiments are noted in table 1. The animals were observed for body weight and survival time.

RESULTS

The detailed data of seven experiments with mitomycin C are presented in table 1, and five of these are summarized in tables 2 and 3. The range of therapy schedules includes treatment daily, treatment every 2, 3, 4, or 8 days, or treatment with a priming dose of mitomycin C followed by a series of lower doses on various intermittent schedules.

For daily treatment the range of doses was from 0.5 to 7.0 mg/kg, and the increase in average lifespan over controls (ILS) ranged from 17% to 65%. Survival time characteristically increased with higher doses of mitomycin C, reaching a maximum increase of 65% at a daily dose of 5.3 mg/kg. There was little difference in results between doses of 7.0 and 5.3 mg/kg, suggesting that both were near optimum on this schedule. Where the duration of daily treatment with 3.5 or 5.3 mg/kg was modified, the greatest increases in survival time accompanied treatment of longest duration. ILS for five treatments at 5.3 mg/kg was 65%, versus 48% for three treatments. ILS for seven treatments at 3.5 mg/kg was 48%, versus 36% or 42% for four treatments.

With treatment every 2 days at doses ranging from 0.8 to 7.0 mg/kg, the mean ILS ranged from 20% to 67%. The greatest increase in survival time was with doses of 7.0 mg/kg on Days 1, 3, and 5 after leukemic inoculation. This outcome is probably near optimal, since in other experiments (table 1, expt F, group 3; expt G1, group 2; expt G2, group 2) this dosage and schedule did elicit more marked toxicity. In general, the greatest survival times were achieved with higher dosages on this schedule. In one experiment an ILS of 52% was achieved with a dose of 1.5 mg/kg, but higher dose levels were not tested in that experiment.

With treatment every 3 days at daily doses ranging from 0.8 to 7.0 mg/kg, the range of ILS was from 17% to 50% with the greatest increase in survival time occurring at a dose of 5.3 mg/kg. In the dose range of 3.5–7.0 mg/kg the ILS values were relatively stable.

With treatment every 4 days at daily doses of 1.5–7.0 mg/kg, ILS ranged from 14% to 59%, with the two greatest increases in survival time occurring at 3.5 and 7.0 mg/kg (the highest dose), again indicating stability over the 3.5–7.0-mg/kg dose range.

With treatment every 8 days at doses of 1.5–7.0 mg/kg, the range of ILS was 5%–34%. Stability again occurred over the 3.5–7.0-mg/kg dose range.

Thus, with treatment daily or every 2, 3, or 4 days, the maximum ILS in the range of doses employed was relatively narrow (maximum ILS for daily treatment, 65%; for every 2 days, 67%; for every 3 days, 50%; for every 4 days, 59%). This suggests that in the range of these dosage schedules there is no definitive schedule dependency in the L1210 system for mitomycin C. However, with treatment every 8 days, somewhat inferior increases in survival time (maximum ILS 34%) were achieved.

Although the data relate primarily to a single experiment, the results summarized in table 3 suggest that use of a priming dose of mitomycin C followed by a series of lower doses administered on an intermittent 4-day schedule may provide some advantage in therapy. On this priming-dose schedule there were two instances in which increases in survival time of over 70% were achieved: priming dose of 5.3 mg/kg followed by 2.3 mg/kg given every 4 days (ILS 74%); and priming dose of 5.3 mg/kg followed by 1.5 mg/kg every 4 days

(ILS 77%). With 5.3 mg/kg followed by 3.5 mg/kg, the ILS was 64%. Even when the priming dose of 5.3 mg/kg was given on Day 1 and the second treatment of 1.5 mg/kg was not given until Day 8, an ILS of 73% was achieved. Comparably high ILS values were not obtained in the two priming-dose groups using 2- or 3-day intervals between treatments.

In one experiment (table 1, expt F) in which mitomycin C appeared to be considerably more effective than in the others, treatment with 1.5 mg/kg every second day yielded an ILS of greater than 150%. This was attributable, however, to one long term survivor; the remaining four mice in this group showed only small increases in survival time. In this experiment, too, a priming dose of 5.3 mg/kg followed by a dose of 1.5 mg/kg every 4 days (expt F, group 4) provided an effective therapy (ILS 95%), with all mice showing moderate increases. It may be noted that in this experiment the dose of 7 mg/kg every 3 days was toxic, as evidenced by losses in body weight and low survival times.

For more mature mice with higher initial body weights, the therapeutic effectiveness of mitomycin C did not seem to be altered substantially (table 1, expt G1 and G2). The animals in experiment G2 were an average of 5 g heavier than those in G1. In both groups, treatment with either 4.6 mg/kg daily or 7.0 mg/kg every second day was toxic. For the schedules tested, the most effective therapy for each set of mice was a dose of 3.1 mg/kg administered every 3 days (G1, ILS 53%; G2, ILS 61%).

DISCUSSION

The current studies show that on standard schedules mitomycin C has only limited schedule dependency in the L1210 leukemia system, and has approximately equal effectiveness when administered on a daily or every 2-, 3-, or 4-day schedule. These results agree with observations of Venditti et al for advanced L1210 leukemia (14) and with data obtained in the screening program of Drug Research and Development (DR&D) (formerly Cancer Chemotherapy National Service Center) for early L1210 leukemia[6] in which an essential lack of schedule dependency was observed. For the schedules employed by DR&D, single dose daily, single dose administered once, treatment every 3 hours for a single day, single dose every fourth day, and treatment every 3 hours every 4 days gave essentially equal activity when started 1 day after leukemic inoculation. However, the current experiments and the data of DR&D show a loss of therapeutic effectiveness when the drug was administered every 7 or 8 days. To some extent this may reflect only the limited efficacy of single-dose treatment, since a schedule with a long interval between treatments is essentially a single-dose treatment schedule. Also, there was some indication in both studies that within limits the survival time could be increased by an increase in the number of treatments on a daily schedule. These observations do suggest at least some limited schedule dependency for mitomycin C. Using mice with Ehrlich ascites tumor, Sokoloff observed that therapy in which the drug was administered daily for 2 days on an intermittent 3- or 4-day schedule was more effective than daily treatment (15). However, in the current study, one group (table 1, expt A, group 18) that received intermittent treatment on Days 1, 2, 8, and 9 after leukemic inoculation had an ILS of only 32%, indicating no advantage for such a schedule.

Also using mice with Ehrlich ascites carcinoma, Hata obtained better results with single treatment on 1 day than with repeated small doses given over an extended period (16). Yet, for mice with subcutaneous solid Ehrlich carcinoma, a 7-day treatment schedule appeared to be more effective than either a 3-day or a daily schedule.

Thus, mitomycin C is potentially schedule-dependent, and the degree of dependency may vary with the tumor system employed as well as with factors such as the site of tumor growth. The fact that the stage of growth of the disease may alter scheduling characteristics has been illustrated with the folic acid antagonist methotrexate (8).[7] With methotrexate, an intermittent schedule provided a ther-

[6] DR&D. Unpublished observations.

[7] Methotrexate: NSC-740; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-.

apeutic advantage over daily treatment for early L1210 leukemia, but there was a loss in therapeutic efficacy for the intermittent schedule in the treatment of advanced disease. However, if the number of cells in an animal with advanced disease is reduced by a priming dose with a cytotoxic agent such as cyclophosphamide or BCNU,[a] the intermittent schedule may again become effective (17,18). In addition, Straus et al (19) have shown that a high priming dose of methotrexate followed by a series of lower doses provides a therapeutic advantage over treatment with a constant dose level of the drug.

In a similar manner, treatment with a high priming dose of mitomycin C followed by lower doses administered on an intermittent schedule appeared to improve the therapeutic effectiveness of the drug. Since mitomycin C acts as an alkylating agent interfering with DNA synthesis (20), the initial priming dose could be expected to reduce the leukemic cell population extensively. This possibility is indicated by the DR&D data showing effectiveness of the drug on single treatment. Both reduction of dosage after the priming dose and use of an intermittent schedule may be necessary to reduce the limiting effect of drug toxicity for the host. Thus, the limited schedule dependency of mitomycin C appears to become more manifest with further consideration of factors limiting drug effectiveness.

Combination of mitomycin C with other drugs has resulted in improved therapeutic effectiveness both in the laboratory and the clinic (21,22). While no outstandingly successful therapy employing mitomycin C has been demonstrated in the present studies, additional work in which schedules and dose levels of the agent, alone or in combination with other agents, are further manipulated may produce such results.

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[a] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

BCNU: NSC-409962; CAS reg. No. 154-93-8; 1,3-bis(2-chloroethyl)-1-nitroso-.

TABLE 1.—Schedule dependency tests of mitomycin C against mouse L1210 leukemia*

Group No.	Dose (mg/kg)	Day of injection	Average body weight (g)			Day of death	Average survival time (days)	ILS (%)
			Day 1	Day 5	Day 9			
			Experiment A					
1†	7.0	1,2,3	21.2	20.6	21.6	12,12,12,12	12.0	50
2	5.3	1,2,3,4,5	21.6	21.3	22.0	12,12,14,14,14	13.2	65
3	5.3	1,2,3,4	21.6	21.2	24.0	11,12,12,13,13	12.2	52
4	5.3	1,2,3	21.2	21.0	23.3	11,11,12,12,13	11.8	48
5	3.5	1,2,3,4,5,6,7	21.5	20.9	20.8	10,11,12,13,13	11.8	48
6	3.5	1,2,3,4,5	21.3	20.4	22.1	11,11,11,11,12	11.2	40
7	3.5	1,2,3,4	20.9	20.1	22.0	10,11,12,12,12	11.4	42
8	7.0	1,3,5	21.1	20.7	20.7	11,12,14,14,16	13.4	67
9	5.3	1,3,5,7	22.2	22.3	22.0	10,11,12,12,14	11.8	48
10	7.0	1,4,7	21.0	21.4	19.8	9,11,12,12,13	11.4	42
11	5.3	1,4,7,10	20.5	19.9	20.8	11,11,11,12,15	12.0	50
12	7.0	1,5,9	21.7	22.8	23.9	12,12,12,12,13	12.2	52
13	5.3	1,5,9	21.3	21.6	22.3	11,11,11,12,13	11.6	45
14	7.0	1,9	21.9	23.5	26.5	9,9,11,11,13	10.6	32
15	5.3	1,9	20.5	21.9	24.1	8,9,10,11,12	10.0	25
16	5.3	1	22.0	22.4	23.4	10,10,10,11,14	11.0	38
	1.5	3,5,7,9,11,13						
17	5.3	1	21.2	21.5	24.3	10,11,11,11,12	11.0	38
	1.5	4,7,10						
18	5.3	1,2,8,9	22.3	23.1	25.9	10,10,10,11,12	10.6	32
19	Saline	1,3,5,7,9	22.0	25.0	—	8,8,8,8,8	8.0	—
			Experiment B					
1	3.5	1,2,3,4	22.1	21.2	21.6	9,10,10,13,15	11.4	36
2	2.3	1,2,3,4,5,6	24.3	23.9	23.5	9,10,10,10,11	10.0	20
3	1.5	1,2,3,4,5,6,7	24.1	24.8	24.7	9,9,10,10,13	10.4	24
4	3.5	1,3,5,7,9	24.8	23.8	24.3	10,11,11,11,13	11.2	33
5	2.3	1,3,5,7,9	24.1	24.6	25.7	9,10,10,10,11	10.0	20
6	1.5	1,3,5,7,9	25.3	25.0	25.0	10,10,10,10,10	10.0	20
7	3.5	1,4,7,10	22.8	20.0	21.3	10,11,12,12,12	11.4	36
8	2.3	1,4,7,10	24.7	24.2	26.3	10,10,10,11,11	10.4	24
9	1.5	1,4,7,10	23.2	22.7	23.7	9,9,9,10,11	9.8	17
10	3.5	1,5,9	23.8	24.8	25.8	9,9,11,11,12	10.4	24
11	2.3	1,5,9	23.6	24.7	25.8	9,9,10,10,13	10.2	21
12	1.5	1,5,9	24.4	24.6	23.8	9,9,10,10,10	9.6	14
13	3.5	1,9	24.3	24.4	25.5	9,10,10,10,12	10.2	21
14	2.3	1,9	24.8	25.6	26.3	9,9,9,10,10	9.4	12
15	1.5	1,9	24.1	24.4	—	8,9,9,9,9	8.8	5
16	Saline	1,3,5,7	24.6	25.5	—	8,8,8,9,9	8.4	—
			Experiment C					
1	1.5	1,2,3,4,5,6,7	22.7	23.0	23.1	10,11,11,11,12	11.4	39
2	1.0	1,2,3,4,5,6,7	22.7	23.4	24.4	10,10,10,11,12	10.6	29
3	0.8	1,2,3,4,5,6,7	22.4	25.7	24.9	9,10,10,10,11	10.0	22
4	0.5	1,2,3,4,5,6,7	23.4	25.4	28.2	9,9,10,10,10	9.6	17
5†	1.5	1,3,5,7,9,11	26.6	27.8	28.1	12,12,13,13	12.5	52
6†	0.8	1,3,5,7,9	18.6	21.2	23.2	10,10,10,10	10.0	22
7†	1.5	1,4,7,10	27.1	27.8	29.8	10,11,12,12	11.2	37
8†	0.8	1,4,7,10	18.7	20.4	23.3	9,9,10,11	9.8	19
9	Saline	1,2,3,4,5,6,7	23.1	25.2	—	8,8,8,8,9	8.2	—
10	No injection	—	22.6	24.8	—	8,8,8,8,9	8.2	—

*L1210 leukemia cells were carried in DBA/2 male mice; experiments were conducted in CDF_1 male hybrids (BALB/c female × DBA/2 male). Leukemic inoculum = 10^5 cells injected ip. Treatment was ip.
†Four mice per group.

TABLE 1.—Schedule dependency tests of mitomycin C against mouse L1210 leukemia*—Continued

Group No.	Dose (mg/kg)	Day of injection	Average body weight (g) Day 1	Day 5	Day 9	Day of death	Average survival time (days)	ILS (%)
			Experiment D					
1	1.5	1,3,5,7,9	18.9	19.9	19.6	10,11,12,12,13	11.8	40
2	5.3	1,4	19.3	17.7	17.5	9,10,11,12,12	10.8	29
3	Saline	1,3,5,7,9	19.0	22.2	20.5	7,8,8,9,10	8.4	—
			Experiment E					
1	1.5	1,2,3,4,5,6,7	24.5	22.4	22.5	11,11,11,12,12	11.4	46
2	3.5	1,4,8,12	23.9	22.7	23.3	9,12,13,14,14	12.4	59
3	3.5	1,8	24.2	24.2	28.4	9,9,10,10,13	12.0	34
4	5.3	1	24.3	22.8	27.7	9,10,10,15,20	12.8	64
	3.5	4,8,12,16						
5	5.3	1	23.8	21.7	22.0	13,13,13,13,16	13.6	74
	2.3	4,8,12						
6	5.3	1	24.0	22.4	22.7	12,13,14,14,16	13.8	77
	1.5	4,8,12						
7	3.5	1	23.1	22.2	24.1	11,11,12,12,13	11.8	51
	2.3	4,8,12						
8	3.5	1	23.9	23.3	25.8	10,11,11,11,12	11.0	42
	1.5	4,8						
9	5.3	1	23.5	22.8	24.0	7,8,10,15,15	10.6	39
	3.5	8						
10	5.3	1	23.8	22.0	23.8	10,10,10,14,14	11.6	52
	2.3	8						
11	5.3	1	25.3	22.8	26.4	11,12,13,13,17	13.2	73
	1.5	8						
12	3.5	1	22.7	22.3	25.7	10,10,11,13,16	12.0	58
	2.3	8						
13	3.5	1	23.7	23.1	27.0	8,11,12,13,13	11.4	50
	1.5	8						
14	Saline	1,8	23.3	26.5	—	7,7,8,8,8	7.6	—
15	Saline	1,4,8	23.6	25.9	—	7,7,8,8,9	7.8	—
16	Saline	1,2,3,4,5,6,7	24.8	26.7	27.5	7,7,8,8,9	7.8	—
			Experiment F					
1	1.5	1,3,5,7,9,11	20.4	19.7	19.2	12,12,13,13,>50	>20	>150
2	3.5	1,3,5,7	19.8	19.2	17.8	11,13,15,15,15	13.8	72
3	7.0	1,4,7	20.5	18.8	15.5	8,8,9,9,10	8.8	10
4	5.3	1	19.8	18.2	18.1	15,15,15,16,17	15.6	95
	1.5	5,9,13						
5	Saline	1,3,5,7	20.3	22.6	—	8,8,8,8,8	8.0	—
			Experiment G1					
1	4.6	1,2,3,4,5	24.2	23.1	24.9	7,7,7,7,7	7.0	–21
2	7.0	1,3,5	25.0	22.8	—	7,7,7,7,8	7.2	–20
3	1.1	1,3,5,7,9,11	25.9	25.1	24.9	10,11,12,12,14	11.8	31
4	3.1	1,4,7,10	25.9	25.1	24.9	12,13,14,14,16	13.8	53
5	4.6	1	25.2	24.5	24.7	12,12,12,13,15	12.8	42
	1.1	5,9,13						
6	Saline	1,3,5,7	25.1	26.2	23.5	8,9,9,9,10	9.0	—
			Experiment G2					
1†	4.6	1,2,3,4,5	30.5	28.4	—	7,7,7,7	7.0	–25
2†	7.0	1,3,5	31.1	27.9	—	6,7,7,8	7.0	–25
3†	1.1	1,3,5,7,9,11	30.7	30.3	30.1	11,11,12,13	11.8	27
4†	3.1	1,4,7,10	31.4	28.8	30.0	13,14,15,16	14.5	61
5†	4.6	1	31.0	29.2	30.0	9,12,13,13	11.8	27
	1.1	5,9,13						
6†	Saline	1,3,5,7	31.0	31.8	32.3	8,9,10,11	9.3	—

TABLE 2.—Influence of treatment schedule on the antileukemic effectiveness of mitomycin C*

TABLE 2.—Influence of treatment schedule on the antileukemic effectiveness of mitomycin C*

Individual dose (mg/kg)	Treatment schedules									
	Daily		Every 2 days		Every 3 days		Every 4 days		Every 7 or 8 days	
	Treatment days	ILS (%)	Treatment days	ILS (%)	Treatment days	ILS (%)	Treatment days	ILS (%)	Treatment days	ILS (%)
7.0	1–3(A–1)	50	1–5(A–8)	67	1–7(A–10)	42	1–9(A–12)	52	1,9(A–14)	32
5.3	1–5(A–2)	65	1–7(A–9)	48	1–10(A–11)	50	1–9(A–13)	45	1,9(A–15)	25
	1–4(A–3)	52			1,4(D–2)	29				
	1–3(A–4)	48								
3.5	1–7(A–5)	48	1–9(B–4)	33	1–10(B–7)	36	1–9(B–10)	24	1,9(B–13)	21
	1–5(A–6)	40					1,4–12(E–2)	59	1,8(E–3)	34
	1–4(A–7,B–1)	42,36								
2.3	1–6(B–2)	20	1–9(B–5)	20	1–10(B–8)	24	1–9(B–11)	21	1,9(B–14)	12
1.5	1–7(B–3,C–1,E–1)	24,39,46	1–11(C–5)	52						
			1–9(B–6,D–1)	20,40	1–10(B–9,C–7)	17,37	1–9(B–12)	14	1,9†(B–15)	5
1.0	1–7(C–2)	29								
0.8	1–7(C–3)	22	1–9(C–6)	22	1–10(C–8)	19				
0.5	1–7(C–4)	17								

*Data are summarized from table 1; experiment and group numbers are in parentheses.

†Because of death, no mice received treatment on Day 9. In other groups, last day shown is day of actual last treatment, either because of death or because of scheduled termination of treatment.

TABLE 3.—Influence of a priming dose on the antileukemic effectiveness of mitomycin C*

Priming dose Day 1 plus treatment every 2 days from Day 3			Priming dose Day 1 plus treatment every 3 days from Day 4			Priming dose Day 1 plus treatment every 4 days from Day 4			Priming dose Day 1 plus treatment on Day 8		
Individual dose	Treatment days	ILS (%)	Individual dose	Treatment days	ILS (%)	Individual dose	Treatment days	ILS (%)	Individual dose	Treatment days	ILS (%)
						5.3 3.5	1 4–12(E–4)	64	5.3 3.5	1 8(E–9)	39
						5.3 2.3	1 4–12(E–5)	74	5.3 2.3	1 8(E–10)	52
5.3 1.5	1 3–13(A–16)	38	5.3 1.5	1 4–10(A–17)	38	5.3 1.5	1 4–12(E–6)	77	5.3 1.5	1 8(E–11)	73
						3.5 2.3	1 4–12(E–7)	51	3.5 2.3	1 8(E–12)	58
						3.5 1.5	1 4–8(E–8)	42	3.5 1.5	1 8(E–13)	50

*Data are summarized from table 1; experiment and group numbers are in parentheses.

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Some Structure-Activity Relationships for Mitomycin C (NSC-26980) Derivatives in the Treatment of L1210 Leukemia [1]

R. Kojima,[2] J. Driscoll,[3] N. Mantel, [4] and A. Goldin [5]

SUMMARY

A series of structural analogs of mitomycin C, including mitosanes, mitosenes, and N_4–C_{9a} open-ring compounds, were tested for extent of activity against L1210 leukemia. With mitomycin C as a standard, structure-activity analyses were conducted, taking into account the toxicity as reflected in optimal dosage and the survival time of the animals. The comparisons were made employing single-dose treatment over a series of dose levels with each drug. Of the compounds tested, mitomycin C and porfiromycin were the most effective in increasing the survival time of the leukemic mice, the optimal dose of the latter being considerably higher. The various structural derivatives showed a wide range of toxicity, and the alterations in therapeutic effectiveness ranged from minimal decreases to complete loss of activity. The wide range of activity in relation to structure suggests that additional modification and investigation of the mitomycin class of compounds may lead to improved therapeutic effectiveness.

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Although mitomycin C is active against a broad spectrum of animal tumors (1,2) and has been used to treat neoplasia in Japan and the United States (3,4), its use has been limited by the manifestation of severe bone marrow depression and gastrointestinal damage (5). Since mitomycin C has demonstrated clinical activity against chronic myelogenous leukemia, solid tumors (including tumors of the colon, breast, lung, stomach, pancreas, and liver), Hodgkin's disease, lymphoma, etc (3,4), it was thought that structural alteration of the drug might reduce toxicity and retain or increase antitumor effect.

The mitomycins are a group of substances isolated from fermentation filtrates of *Streptomyces caespitosus*. Mitomycin A and B [6] were first isolated by Hata et al (6). Wakaki and co-workers isolated mitomycin C and a series of additional fractions (7). Mitomycin derivatives have been used in antitumor studies against Hirosaki ascites sarcoma (8) and Sarcoma 180 (9), and a number of the derivatives were as effective as (or possibly more effective than) mitomycin C. The synthesis and characterization of the biologic activity

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[2] Kyowa Hakko Kogyo Company, Ltd., Tokyo, Japan. Work performed as guest worker in Division of Cancer Treatment (DCT), National Cancer Institute (NCI), Bethesda, Md.

[3] Drug Development Branch, Drug Research and Development (DR&D), DCT, NCI, Bethesda, Md.

[4] Biometry Branch, NCI, Bethesda, Md.

[5] DR&D, DCT, NCI, Bethesda, Md.

[6] Mitomycin A: NSC-75986; CAS reg. No. 4055-39-4; (azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-6,8*a*-dimethoxy-5-methyl-, carbamate).

Mitomycin B: NSC-75987; CAS reg. No. 4055-40-7; (azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8,8*a*,8*b*-hexahydro-8*a*-hydroxy-8-(hydroxymethyl)-6-methoxy-1,5-dimethyl-, 8-carbamate).

of additional mitomycin derivatives have contributed further information concerning the structure-activity relationships of this class of compounds (10–13).

Our studies were the initial step in a program to characterize the structure-activity relationships of mitomycin derivatives in the treatment of mouse L1210 leukemia. For this purpose compounds were selected with various substituents on the three potentially carcinostatic groupings, quinone, aziridine, and carbamoyloxymethyl, for mitosane and mitosene derivatives. Two compounds were included in which the N_1–C_{9a} bond had been broken.

METHODS

The standard screening program methods of the NCI's Drug Research and Development program were employed. L1210 leukemia was maintained in DBA/2 mice and was implanted intraperitoneally (ip) (10^5 cells) in CDF_1 hybrid male (BALB/c female × DBA/2 male) mice. Mitomycin C was obtained from the Bristol Laboratories and the Kyowa Hakko Kogyo Company, Ltd. The mitomycin derivatives were obtained from the Kyowa Hakko Kogyo Company, Ltd. The drugs were prepared for injection in saline, 0.5% carboxymethylcellulose, or acetone–Tween-80–saline. The drugs were administered ip as a single injection 1 day after leukemic inoculation. The numbers of animals employed are indicated in the individual experiments. The animals were observed for body weight and survival time.

RESULTS

Detailed data from six experiments with mitomycin C and 19 of its structural analogs are presented in table 1, which shows the average weight of surviving animals on Days 1, 5, and 7 after tumor inoculation for each dose tested. Individual and average survival times are also shown, with the average re-expressed as a percentage increase in lifespan (ILS) over vehicle-treated or untreated controls in the same experiment. Structure-activity data are summarized in tables 2–4, and optimal dose-survival time data are shown in figure 1.

The largest ILS value and its corresponding dose were determined for each compound tested (tables 2–4), and these values are plotted as maximum relative survival time versus optimal dose in figure 1. (Where two dose levels yielded the same ILS, the one corresponding to the higher average body weight on Day 7 was used.) In tables 2–4 and figure 1 we identify instances where the optimal dose was either the lowest or highest of those used, because the true optimal dose in these cases may be outside our dosage range. For each plotted point in figure 1, we identify the compound tested, the class of mitomycin C analogs to which it belongs, and the test vehicle. Data for five compounds not included in table 1 are presented in summary form in figure 1 and tables 2 and 3 (four compounds in table 2 and one in table 3). These compounds are footnoted in the tables, and data for them are shown in the experiment 1 column.

Mitosane Compounds (tables 1, 2; fig 1)

In six experiments the optimal dose of mitomycin C ranged from 3.5 to 7.0 mg/kg. In five of these experiments the ILS ranged from 31% to 77%, with an average of 51%. However, in the sixth experiment the ILS was greater than 92%.

Aliphatic substitution on the amino group in the 7 position (X) appeared to decrease drug toxicity for the host as reflected in an increase in optimal dose relative to mitomycin C, but this was accompanied by a moderate to four-fold reduction in antileukemic effectiveness (ie, the survival time increase was not as extensive as for mitomycin C). Substitution of a normal propyl or butyl group on the 7-amino position (NSC-123115 and NSC-134716) yielded optimal doses of 23.2 and 9.5 mg/kg and increases in survival time of only 20%. Substitution of a β-hydroxy ethyl group on the 7-amino position (NSC-123108) yielded an optimal dose of 23.2 mg/kg, with an ILS of only 12%.

With a methoxy group substituted for the amino group in the X position plus a benzoyl group substituted for the hydrogen in the Z position (NSC-134722), there also appeared to be some decrease in toxicity as reflected in an

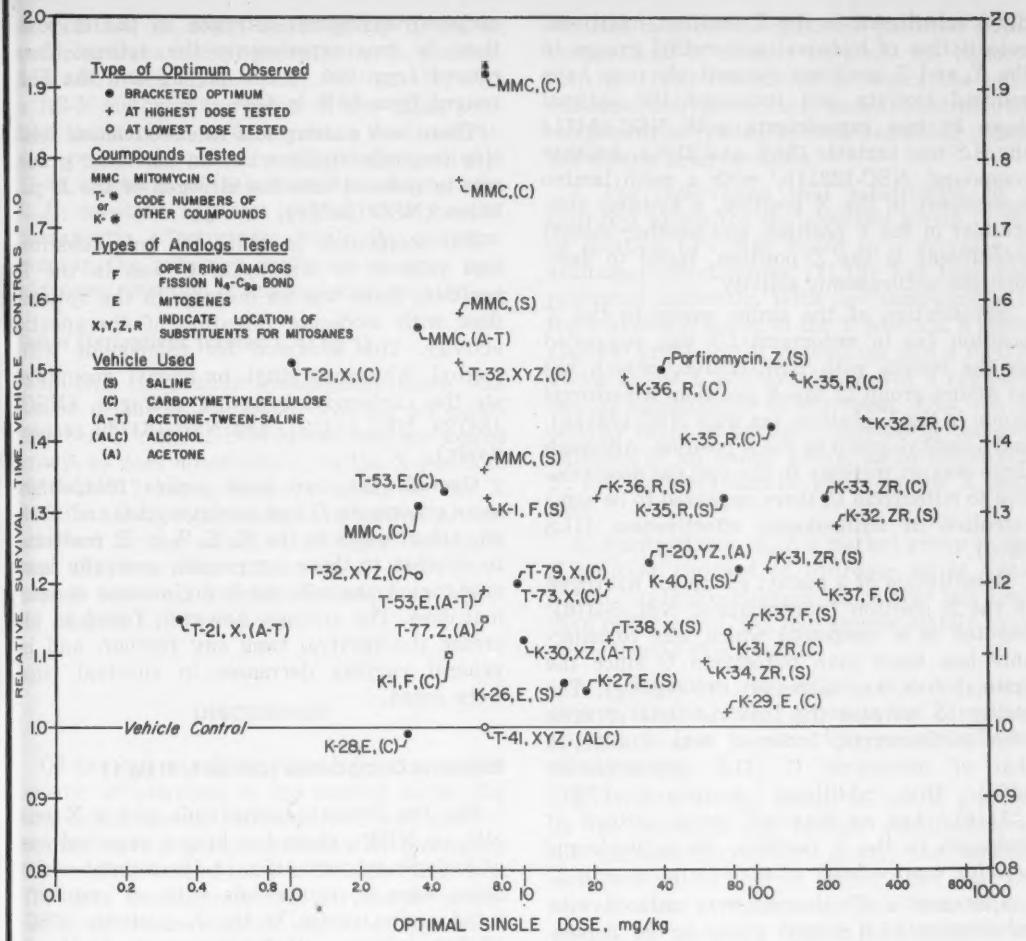

FIGURE 1.—Relative survival time at optimal single dose levels for mitomycin C derivatives.

increase in optimal dose and a loss of antileukemic effectiveness.

In contrast to compounds with simple aliphatic substituents, substitution of an aziridine moiety for the amino group in the 7 position (NSC-134713) in two experiments resulted in a substantial increase in toxicity as reflected in a decrease in the optimal dose. The increase in survival time was variable, ranging from 15% to 52% at the optimal dose, but it is not clear if this difference is attributable to the difference in vehicle in the two experiments.

It has been reported that substitution of a hydroxyl group for the methoxy group in the 9*a* position (Y) of mitomycin C results in a decrease in both antitumor and antibacterial activity (11,12), but we tested no compounds with substitution only in the Y position. One compound (NSC-134714) has a hydroxyl group in the Y position and a methyl group in the Z position. It also has an aziridinyl group instead of the amino group in the X position, thereby resembling NSC-134713. NSC-134714 did not appear to be quite as toxic as NSC-134713, suggesting that with an aziri-

dinyl substituent in the X position, additional substitution of hydroxyl and methyl groups in the Y and Z positions respectively may have reduced toxicity and increased the optimal dose. In two experiments with NSC-134714 the ILS was variable (52% and 21%). Another compound, NSC-123110,[†] with a methylamino substituent in the X position, a hydroxy substituent in the Y position, and another methyl substituent in the Z position, failed to demonstrate antileukemic activity.

Substitution of the amino group in the X position (as in mitomycin C) was suggested by the results with NSC-123106,[†] which has an amino group in the X position, a hydroxyl group in the Y position (as with NSC-123110), and a methyl group in the Z position. Although there was an increase in the optimal dose relative to mitomycin C, there appeared to be some retention of antileukemic effectiveness (ILS 23%).

Substitution of a methyl group for hydrogen in the Z position (porfiromycin, NSC-56410)[†] resulted in a compound which was considerably less toxic than mitomycin C since the optimal dose was increased (40 mg/kg). The ability to increase the survival time of mice with porfiromycin, however, was similar to that of mitomycin C (ILS approximately 50%). One additional compound (NSC-123116),[†] has an octanoyl group instead of hydrogen in the Z position. Its antileukemic activity was reduced relative to mitomycin C.

Therapeutic effectiveness was reduced with substitution of a methyl group in the Z position and introduction of a hydroxyl group in the Y position. This occurred as reported above with NSC-123110 and NSC-123106.

In the porfiromycin series, changes in the R position gave optimal doses as high as or higher than those observed with porfiromycin. NSC-134723 has a methyl substituent on the carbamoyloxymethyl nitrogen. The optimal dose in two experiments ranged from 75 to 112 mg/kg and the ILS ranged from 13% to 22%. With an ethyl substituent on the carbamoyloxymethyl) nitrogen (NSC-134725), the optimal dose was 200 mg/kg and the ILS was 32%. NSC-134724 is similar to porfiromycin but has a β-hydroxy ethyl substituent on the carbamoyloxymethyl nitrogen in the R position. In two experiments the optimal dose ranged from 225 to 300 mg/kg and the ILS ranged from 28% to 43%.

There was a sharp loss in effectiveness relative to porfiromycin when an aziridino group was introduced onto the nitrogen of the R position (NSC-134726).

For compounds in which the only substitution relative to mitomycin C was in the R position, there was an increase in the optimal dose with moderate retention of therapeutic activity. This occurred for compounds with methyl, β-hydroxy ethyl, or phenyl groupings on the carbamoyloxymethyl nitrogen (NSC-134728, NSC-134727, and NSC-134730 respectively).

Overall, the two most active compounds were mitomycin C and porfiromycin, and various substituents in the X, Y, Z, or R positions in relation to these compounds generally lowered toxicity as reflected in an increase in optimal dose. The analogs, however, failed to increase the survival time any further, and in general varying decreases in survival time were noted.

Mitosene Compounds (tables 1, 3; fig 1)

For the mitosene compounds where X was NH_2 or NHEt, there has been a reported loss of biologic activity (12). In the current series there were no compounds with an unsubstituted amino group in the X position. NSC-134721, with an ethylamino group in the X position, a hydroxyl group in the R_1 position, and an acetyl amino group in the R_2 position, was ineffective at the highest dose employed (75 mg/kg). NSC-134720, with a phenylamino group in the X position, a hydroxyl group in the R_1 position, and an acetylamino moiety in the R_2 position, showed apparently complete loss of antileukemic activity.

There were three compounds in this series with a methoxy group in the X position. NSC-134719, with a hydroxyl group in the R_1 position and an *N*-acetyl, *N*-methyl amino group on the R_2 position, showed loss of activity. NSC-134718,[†] with an acetoxy group in the

[†] Prior data of DR&D, DCT, NCI.

R_1 position, an acetyl amino group in the R_2 position, and a methyl group in the R_3 position, was also inactive. However, NSC-123111, with a 1,2-*N*-methylimino group in the R_1,R_2 position (resembling porfiromycin in this respect), did retain definitive antileukemic activity. Thus, removal of the aziridine ring at the R_1,R_2 position appears to lead to a loss of therapeutic effectiveness while its inclusion even in the mitosene configuration may permit some retention of antileukemic activity.

Other Derivatives (tables 1, 4; fig 1)

In two compounds investigated there was fission of the N_4–C_{9a} bond, creating an eight-membered ring. NSC-134729 has an amino group, as does mitomycin C, in the X position. NSC-134717 has a methoxy group in the X position. Both compounds have methyl groups attached to the aziridino nitrogen. Although less effective than mitomycin C, both compounds appeared to have retained some activity against L1210 leukemia.

DISCUSSION

Of the compounds evaluated for chemotherapeutic effectiveness in the current series, the established agents (mitomycin C and porfiromycin) were the most effective in increasing the survival time of mice with L1210 leukemia. The data demonstrate that structural modification of the mitomycin molecule may result in a wide range of activities with respect to both toxicity for the host and antileukemic effectiveness. Although the current studies are limited to single-dose treatment and small numbers of animals because of low drug supply, they may nonetheless serve as a guide for further synthesis and analysis, and the following observations can be made.

1. Aliphatic substitution in the 7-amino position (X) resulted in decreased toxicity (increase in optimal dose) and some reduction in antileukemic effectiveness.

2. Substitution of an aziridinyl group in the 7 position resulted in increased toxicity with apparent retention of antileukemic effectiveness. Substitution at the 7 position (X) which is adjacent to quinone carbonyl has been reported to affect the reduction potential of the quinone and to thereby influence the biologic activity (12). The extent to which the antileukemic activity of the tested 7-substituted compounds is related to their reduction potential awaits determination.

3. The observation that substitution of a hydroxyl group for the methoxy group in the 9*a* position (Y) may result in a decrease in antitumor effectiveness (11,12) has been corroborated indirectly. With one compound having a hydroxyl group in the Y position, a methylamino group in the X position, and a methyl group in the Z position, there was a complete loss of antileukemic effectiveness. This loss of activity could be partially negated by the substitution of an amino group, as in mitomycin C, for the methylamino group in the X position.

4. Porfiromycin, with a methyl group in the Z position (instead of hydrogen as in mitomycin C), is a compound which was less toxic than mitomycin C but had approximately equal antileukemic effectiveness.

5. Substitution of either acyl or aroyl groups for the methyl group in the Z position appears to lead to some loss in antileukemic effectiveness.

6. With a methyl group in the Z position on the aziridine and further substitution in the carbamoyloxymethyl group, the optimal dose was as high as or higher than that observed with porfiromycin. This was accompanied by moderate loss in antileukemic effectiveness.

7. There was a marked loss in the effectiveness of porfiromycin with the introduction of an aziridinyl group into the carbamoyloxymethyl moiety.

8. With substitution on the carbamoyloxymethyl moiety only, the optimal dose as compared with mitomycin C generally increased, with moderate retention of therapeutic effectiveness.

9. It has been reported that with an amino or ethyl amino substituent in the X position of the mitosene compounds, there was a loss of antibacterial activity attributable to a lowering of the reduction potential (12). In the current study, two compounds in the mitosene

series with substituted amino groups in the X position lost antileukemic activity. The only mitosene derivative in the limited series tested which appeared to show some antileukemic activity had a methyl aziridino group (1,2-*N*-methylimino group) in the R_1,R_2 position with a methoxy group in the X position.

10. Fission of the N_4–C_{9a} bond resulting in the creation of an eight-membered ring reduced antileukemic effectiveness.

Clearly, a wide range of alteration of the toxicity and antileukemic effectiveness of mitomycin C (and also porfiromycin) results from substitutions in the various positions of the molecule and other structural alterations, and these modifications of the mitomycin molecule are interrelated with respect to the resultant effect. Although no improvement in antileukemic effectiveness over mitomycin C and porfiromycin was observed, the alterations in toxicity and antileukemic effectiveness suggest that additional studies of structural alterations of mitomycin may lead to improved therapeutic effectiveness.

TABLE A.—List of compounds tested

NSC No.	Supplier Code No.	Compound	Molecular formula	CAS registry No.
26980	—	Mitomycin C: azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole-4,7-dione, 6-amino-1,1*a*,2,8,8 *a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbamate (ester)	$N_4O_5C_{15}H_{18}$	50-07-7
56410	—	Porfiromycin: carbamic acid, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-1,5-dimethylazirino-[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7,dione	$N_4O_5C_{16}H_{20}$	801-52-5
123106	T–20	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8*a*-hydroxy-8-(hydroxymethyl)-1,5-dimethyl-, 8-carbamate	$N_4O_5C_{13}H_{16}$	—
123108	T–38	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8,8*a*,8*b*-hexahydro-6-[(2-hydroxyethyl)amino]-8-(hydroxymethyl-, 8*a*-methoxy-5-methyl-, 8-carbamate	$N_4O_6C_{17}H_{22}$	4049-16-5
123110	T–41	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8,8*a*,8*b*-hexahydro-8*a*-hydroxy-8-(hydroxymethyl)-1,5-dimethyl-6-(methylamino)-, 8-carbamate	$N_4O_5C_{16}H_{20}$	—
123111	T–53	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8*b*-tetrahydro-8-(hydroxymethyl)-6-methoxy-1,5-dimethyl-, carbamate (ester)	$N_3O_5C_{16}H_{17}$	—
123115	T–73	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-6-(propylamino)-, carbamate (ester)	$N_4O_5C_{18}H_{24}$	16032-94-3
123116	T–77	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-1-octanoyl-, carbamate (ester)	$N_4O_6C_{23}H_{32}$	—
134713	T–21	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-(1-aziridinyl)-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbamate (ester)	$N_4O_5C_{17}H_{20}$	13164-87-9
134714	T–32	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-(1-aziridinyl)-1,1*a*,2,8,8*a*,8*b*-hexahydro-8*a*-hydroxy-8-(hydroxymethyl)-1,5-dimethyl-, carbamate (ester)	$N_4O_5C_{17}H_{20}$	13164-89-1
134716	T–79	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-(butylamino)-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbamate (ester)	$N_4O_5C_{19}H_{26}$	16032-92-1

TABLE A.—List of compounds tested—Continued

NSC No.	Supplier Code No.	Compound	Molecular formula	CAS registry No.
134717	K–1	1*H*-Azirino[2,3-*f*][1]benzazocine-4,7,9(8*H*)-trione, 1*a*,2,3,-9*a*-tetrahydro-8-(hydroxymethyl)-6-methoxy-3,5-dimethyl-, carbamate (ester)	$N_2O_6C_{14}H_{15}$	—
134718	K–26	Acetamide, *N*-[2,3,5,8-tetrahydro-1-hydroxy-9-(hydroxymethyl)-7-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indol-2-yl)-, diacetate (ester)	$N_2O_8C_{20}H_{22}$	1254-17-7
134719	K–27	Acetamide, *N*-[2,3,5,8-tetrahydro-1-hydroxy-9-(hydroxymethyl)-7-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indol-2-yl]-*N*-methyl-, 9-carbamate	$N_3O_7C_{15}H_{17}$	—
134720	K–28	Acetamide, *N*-[7-anilino-2,3,5,8-tetrahydro-1-hydroxy-9-(hydroxymethyl)-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]-indol-2-yl]-, 9-carbamate	$N_4O_6C_{22}H_{22}$	20956-77-8
134721	K–29	Acetamide, *N*-[7-(ethylamino)-2,3,5,8-tetrahydro-1-hydroxy-9-(hydroxymethyl)-6-methyl-5,8-dioxo-1*H*-pyrrolo-[1,2-*a*]indol-2-yl]-, 9-carbamate	$N_4O_6C_{18}H_{22}$	20956-75-6
134722	K–30	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 1-benzoyl-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-6,8a-dimethoxy-5-methyl-, carbamate (ester)	$N_3O_7C_{23}H_{23}$	4049-10-9
134723	K–31	Carbamic acid, methyl-, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{17}H_{22}$	—
134724	K–32	Carbamic acid, (2-hydroxyethyl)-, ester with 6-amino-1,-1*a*,2,8,8*a*,8*b*-hexahydro-8-hydroxymethyl)-8*a*-methoxy-1,-5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{18}H_{24}$	—
134725	K–33	Carbamic acid, ethyl-, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{18}H_{24}$	—
134726	K–34	1-Aziridinecarboxylic acid, ester with 6-amino-1,1*a*,2,8,-8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{18}H_{24}$	—
134727	K–35	Carbamic acid, (2-hydroxyethyl)-, ester with 6-amino-1,-1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{17}H_{22}$	—
134728	K–36	Carbamic acid, methyl-, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione	$N_4O_6C_{16}H_{20}$	—
134729	K–37	Carbamic acid, methyl-, ester with 6-amino-1*a*,3,8,9*a*-tetrahydro-8-(hydroxymethyl)-1,3,5-trimethyl-1*H*-azirino[2,-3-*c*][1]benzazocine-4,7,9(2*H*)-trione	$N_4O_6C_{17}H_{22}$	—
134730	K–40	Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbanilate (ester)	$N_4O_6C_{21}H_{22}$	—

TABLE 1.—L1210 antileukemic activity of mitomycin C and structural analogs of mitomycin C

Drug	Dose (mg/kg)	Average body weight (g) Day 1	Day 5	Day 7	Day of death	Average survival time (days)	ILS (%)
			*Experiment 1**				
NSC-26980	6.75	19.6	19.0	19.3	10,11,13	11.3	36
(Mitomycin C [MMC])	4.5	22.7	23.0	24.3	9,9,9	9.0	8
	2.9	20.3	20.3	21.7	9,11,11	10.3	24
NSC-123108	23.2	19.3	19.0	19.7	8,9,11	9.3	12
(T-38)	15.5	18.0	19.0	20.3	8,8,8	8.0	–4
	10.2	21.7	23.3	24.0	8,8,8	8.0	–4
NSC-123111	6.75	22.7	21.7	21.0	8,8,12	9.3	12
(T-53)	4.5	20.3	21.7	21.7	8,12,13	11.0	33
	2.9	17.0	16.5	17.6	—,8,13	10.5	26
NSC-123115	23.2	19.3	18.0	18.1	9,10,11	10.0	20
(T-73)	15.5	21.0	20.7	20.7	9,9,10	9.3	12
	10.2	23.3	24.0	25.5	8,9,10	9.0	8
Control (untreated)	0	20.7	21.0	22.7	8,8,9	8.3	—
			Experiment 2†				
NSC-26980	5.3	19.7	20.0	21.5	11,12,13	12.0	58
(Mitomycin C [MMC])	3.5	21.7	21.8	24.0	10,11,14	11.7	54
	2.3	19.7	21.5	23.3	9,10,12	10.3	36
NSC-134717	7.0	19.2	18.0	17.5	8,11,11	10.0	32
(K-1)	4.7	20.0	19.5	20.0	8,9,11	9.3	22
	3.1	21.2	22.3	21.5	8,8,9	8.3	9
NSC-134719	25.6	20.7	23.8	—	7,7,7	7.0	–8
(K-27)	18.7	22.5	24.2	24.7	8,8,8	8.0	5
	12.5	22.7	25.0	—	7,7,8	7.3	–4
NSC-134723	112	22.5	22.7	23.8	9,9,10	9.3	22
(K-31)	75	22.2	22.0	24.2	9,9,9	9.0	18
	50	21.7	23.0	23.3	7,8,9	8.0	5
NSC-134724	225	23.6	21.8	22.3	9,10,10	9.7	28
(K-32)	150	21.5	22.2	24.7	9,9,10	9.3	22
	100	23.5	23.8	24.8	8,9,10	9.0	18
NSC-134726	60	21.3	23.3	24.8	8,8,9	8.3	9
(K-34)	40	20.3	23.3	—	7,7,8	7.3	–4
	26.6	20.3	22.8	—	7,8,9	8.0	5
NSC-134727	114	22.0	20.2	21.2	9,9,11	9.7	28
(K-35)	74	25.3	24.8	26.8	10,10,10	10.0	32
	49.3	23.0	23.0	25.5	9,9,10	9.3	22
NSC-134728	20.6	19.3	21.3	21.7	8,10,12	10.0	32
(K-36)	13.7	21.2	22.3	26.0	8,9,9	8.7	14
	9.2	20.8	22.5	24.5	8,9,9	8.7	14
NSC-134729	93.5	18.7	22.8	23.5	8,9,9	8.7	14
(K-37)	62.5	21.5	24.7	24.7	8,8,9	8.3	9
	41.6	19.7	22.0	22.7	8,8,8	8.0	5

*L1210 inoculum = 10^5 cells injected ip on Day 0; treatment on Day 1 only, ip. Vehicle for MMC and T-38 = saline; vehicle for T-53 and T-73 = 0.5% CMC.

†L1210 inoculum = 10^5 cells injected ip on Day 0; treatment on Day 1 only, ip. Vehicle = saline.

TABLE 1.—L1210 antileukemic activity of mitomycin C and structural analogs of mitomycin C — Continued

Drug	Dose (mg/kg)	Average body weight (g) Day 1	Day 5	Day 7	Day of death	Average survival time (days)	ILS (%)
NSC-134730	127	21.2	22.8	24.2	9,9,9	9.0	18
(K-40)	85	22.7	24.0	26.7	9,9,10	9.3	22
	57	20.8	23.7	25.8	7,8,8	7.7	1
Control (saline)	0	19.5	22.2	23.3	7,7,7,7,8,8,8,8,8	7.6	—
			Experiment 3‡				
NSC-26980	5.25	19.2	16.8	16.6	14,14,15	14.3	77
(Mitomycin C [MMC])	3.5	21.0	18.8	18.6	9,13,16	12.7	57
	2.3	20.2	17.7	17.6	8,9,10	9.0	11
NSC-134720	4.7	19.7	19.3	—	7,7,9	7.7	–5
(K-28)	3.1	21.0	23.2	23.8	8,8,8	8.0	–1
	2.0	22.6	23.8	—	6,7,8	7.0	–14
NSC-134721	75	18.5	18.7	20.3	8,8,9	8.3	2
(K-29)	50	21.7	21.0	24.2	8,8,8	8.0	–1
	33	20.7	21.3	23.5	8,8,8	8.0	–1
NSC-134725	300	19.5	17.0	17.5	6,—,12	9.0	11
(K-33)	200	19.5	18.5	19.0	10,11,11	10.7	32
	133	19.3	18.5	19.5	9,10,10	9.7	20
NSC-134729	187	20.3	20.2	20.0	9,10,10	9.7	20
(K-37)	125	20.5	22.2	22.0	8,8,9	8.3	2
	83	21.7	23.3	23.2	8,8,10	8.7	7
NSC-134713	1.5	20.3	18.0	17.0	7,10,11	9.3	15
(T-21)	1.0	20.8	19.7	18.7	11,13,13	12.3	52
	0.6	21.0	19.2	18.7	9,13,14	12.0	48
NSC-134714	5.25	20.7	17.2	16.3	10,13,14	12.3	52
(T-32)	3.5	21.3	18.2	17.3	9,11,13	11.0	36
	2.3	21.8	20.0	20.7	8,10,13	10.3	27
NSC-134716	14.3	21.3	21.8	21.8	8,8,9	8.3	2
(T-79)	9.5	20.5	20.0	23.0	9,9,11	9.7	20
	6.3	22.2	22.2	23.7	8,8,9	8.3	2
Control (CMC)	0	22.2	23.5	24.2	8,8,8,8,8,8,8,8,9	8.1	—
			Experiment 4§				
NSC-26980	5.3	24.4	23.4	23.9	11,11,12,12	11.5	44
(Mitomycin C [MMC])	3.5	24.9	24.4	26.1	10,11,11,18	12.5	56
	2.3	22.6	23.3	25.3	9,10,11,18	12.0	50
	1.75	24.4	25.3	28.0	9,10,11,12	10.5	31
	1.15	25.4	28.1	31.3	9,9,11,11	10.0	25
	0.87	24.8	26.3	27.6	7,9,9,10	8.8	10
NSC-134713	1.5	24.3	—	—	3,3,3,3	3.0	–62
(T-21)	1	24.1	23.5	24.5	4,4,8,10	6.5	–19
	0.66	23.8	—	—	4,5,5,5	4.8	–40
	0.44	24.1	22.0	20.4	6,6,6,6	6.0	–25
	0.3	24.0	22.0	22.5	6,7,11,13	9.2	15
	0.25	22.4	20.5	21.5	5,7,9,13	8.5	6

‡L1210 inoculum = 10^5 cells injected ip on Day 0; treatment on Day 1 only, ip. Vehicle = 0.5% CMC.
§L1210 inoculum = 10^5 cells injected ip on Day 0; treatment on Day 1 only, ip. Vehicle = acetone–Tween-80–saline.

TABLE 1.—L1210 antileukemic activity of mitomycin C and structural analogs of mitomycin C — Continued

Drug	Dose (mg/kg)	Average body weight (g) Day 1	Day 5	Day 7	Day of death	Average survival time (days)	ILS (%)
NSC-123111	6.75	23.8	23.9	25.9	9,9,9,11	9.5	19
(T-53)	4.5	24.0	24.9	27.9	8,8,9,10	8.8	10
	2.9	23.4	23.7	27.3	7,8,8,11	8.5	6
	2.2	25.1	26.8	28.5	8,8,8,9	8.2	3
NSC-134722	15	23.8	22.3	24.5	8,9,9,10	9.0	12
(K-30)	10	23.8	24.1	25.3	8,9,9,10	9.0	12
	7.5	23.1	24.4	26.4	8,8,9,9	8.5	6
Control (acetone–Tween-80–saline)	0	23.8	25.7	27.8	8,8,8,8 8,8,8,8	8.0	—
			Experiment 5¶				
NSC-26980	7.6	20.3	18.9	17.2	7,10,10,14	10.2	21
(Mitomycin C [MMC])	3.5	21.8	20.9	21.6	8,11,12,13	11.0	31
	1.75	21.1	20.8	22.7	7,9,10,11	9.2	10
	0.87	21.8	23.3	25.0	9,9,9,9	9.0	7
NSC-134717	9.4	21.6	18.3	18.5	5,5,6,11	6.8	–19
(K-1)	4.7	20.4	17.0	18.9	8,8,9,12	9.2	–10
NSC-134723	150	20.8	18.9	18.9	8,9,10,11	9.5	13
(K-31)	75	20.9	19.0	20.1	9,9,10,10	9.5	13
NSC-134724	300	19.9	17.3	16.9	9,12,13,14	12.0	43
(K-32)	150	19.9	19.0	20.6	10,11,11,14	11.5	37
NSC-134727	148	21.4	17.5	18.0	10,11,13,16	12.5	49
(K-35)	74	21.6	18.5	18.6	11,12,12,14	12.2	45
NSC-134728	27.5	19.9	18.4	19.1	10,13,13,14	12.5	49
(K-36)	13.8	19.0	17.0	18.3	9,9,10,10	9.5	13
NSC-134714	7.0	19.9	16.9	17.3	6,10,11,13	10.0	19
(T-32)	3.5	20.6	19.8	21.0	8,9,12,12	10.2	21
Control (CMC)	0	20.6	20.6	21.2	7,8,8,8 8,9,9,10	8.4	—
			Experiment 6¶				
NSC-26980	10.5	19.7	16.9	16.0	9,11,11,12,12	11.0	15
(Mitomycin C [MMC])	7	20.2	17.5	17.2	12,15,17,18,>30	>18.4	>92
	5.3	20.1	18.2	17.9	11,12,13,14,15	13.0	35
	3.5	19.2	17.5	18.0	11,12,12,12,13	12.0	25
	2.3	20.2	20.0	21.8	11,11,11,12,12	11.4	19
NSC-134727	222	20.5	15.3	14.0	6,6,6,15,16	9.8	2
(K-35)	148	20.4	14.7	15.1	5,13,14,15,15	12.4	29
	119	19.8	16.8	16.7	13,13,13,14,15	13.6	42
	74	20.2	18.0	18.1	11,11,13,13,14	12.4	29
	49	19.8	18.6	19.5	10,11,12,13,15	12.2	27
Control (CMC)	0	20.6	22.2	22.7	8,9,10,10,11	9.6	—

¶L1210 inoculum = 10^5 cells injected ip on Day 0; treatment on Day 1 only, ip. Vehicle = 0.5% CMC.

TABLE 2.—Structure-activity relationships: mitosane derivatives

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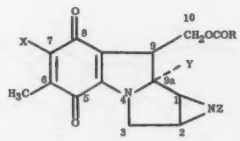


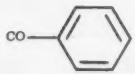
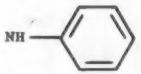
NSC No. (Supplier's Code No.)	Substituents X	Y	Z	R	Expt 1 Optimal dose (mg/kg)	Expt 1 ILS (%)	Expt 2 Optimal dose (mg/kg)	Expt 2 ILS (%)	Expt 3 Optimal dose (mg/kg)	Expt 3 ILS (%)	Expt 4 Optimal dose (mg/kg)	Expt 4 ILS (%)	Expt 5 Optimal dose (mg/kg)	Expt 5 ILS (%)	Expt 6 Optimal dose (mg/kg)	Expt 6 ILS (%)
26980 Mitomycin C	NH_2	OCH_3	H	NH_2	6.75*	36	5.3*	58*	5.25*	77	3.5	56	3.5	31	7	>92
123115 (T-73)	$CH_3(CH_2)_2NH$	OCH_3	H	NH_2	23.2*	20										
134716 (T-79)	$CH_3(CH_2)_3NH$	OCH_3	H	NH_2					9.5	20						
123108 (T-38)	$HOCH_2CH_2NH$	OCH_3	H	NH_2	23.2*	12										
134713 (T-21)		OCH_3	H	NH_2					1.0	52	0.33	15				
134722 (K-30)	CH_2O	OCH_3		NH_2							10	12				
123110 ‡ (T-41)	H_2CHN	OH	CH_2	NH_2	6.6	0										
134714 (T-32)		OH	CH_2	NH_2					5.25*	52			3.5†	21		
123106 ‡ (T-20)	NH_2	OH	CH_2	NH_2	35	23										
56410 ‡ Porfiromycin	NH_2	OCH_3	CH_2	NH_2	40	50										
134723 (K-31)	NH_2	OCH_3	CH_2	$NHCH_3$			112*	22					75†	13		
134725 (K-33)	NH_2	OCH_3	CH_2	$NHCH_2CH_3$					200	32						
134724 (K-32)	NH_2	OCH_3	CH_2	$NHCH_2CH_2OH$			225*	28					300*	43		

TABLE 2.—Structure-activity relationships: mitosane derivatives—Continued

NSC No. (Supplier's Code No.)	Substituents X	Y	Z	R	Expt 1 Optimal dose (mg/kg)	Expt 1 ILS (%)	Expt 2 Optimal dose (mg/kg)	Expt 2 ILS (%)	Expt 3 Optimal dose (mg/kg)	Expt 3 ILS (%)	Expt 4 Optimal dose (mg/kg)	Expt 4 ILS (%)	Expt 5 Optimal dose (mg/kg)	Expt 5 ILS (%)	Expt 6 Optimal dose (mg/kg)	Expt 6 ILS (%)
134726 (K-34)	NH_2	OCH_3	CH_3				60*	9								
123116 ‡ (T-77)	NH_2	OCH_3	$CO(CH_2)_4CH_3$	NH_2	6.6†	15										
134728 (K-36)	NH_2	OCH_3	H	$NHCH_3$			20.6*	32					27.5*	49		
134727 (K-35)	NH_2	OCH_3	H	$NHCH_2CH_2OH$			74	32					148*	49	119	42
134730 (K-40)	NH_2	OCH_3	H				85	22								

*Optimal dose is highest dose tested.

†Optimal dose is lowest dose tested.

‡Data of DR&D, DCT, NCI. Vehicle for porfiromycin = saline; vehicle for NSC-123106 and NSC-123116 = acetone; vehicle for NSC-123110 = acetone and alcohol.

TABLE 3.—Structure-activity relationships: mitosene derivatives

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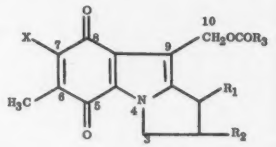
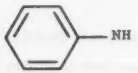
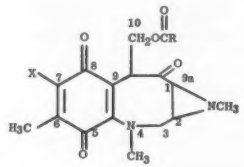


NSC No. (Supplier's code No.)	Substituents				Expt 1		Expt 2		Expt 3		Expt 4	
	X	R_1	R_2	R_3	Optimal dose (mg/kg)	ILS (%)	Optimal dose (mg/kg)	ILS (%)	Optimal dose (mg/kg)	ILS (%)	Optimal dose (mg/kg)	ILS (%)
26980 Mitomycin C					6.75*	36	5.3*	58	5.25*	77	3.5	56
134721 (K-29)	CH_2CH_2NH	OH	$NHCOCH_3$	NH_2					75†	2		
134720 (K-28)		OH	$NHCOCH_3$	NH_2					3.1	−1		
134719 (K-27)	CH_2O	OH	$N(CH_3)COCH_3$	NH_2			18.7	5				
123111 (T-53)	CH_2O			NH_2	4.5	33					6.75*	19
134718† (K-26)	CH_2O	$OCOCH_3$	$NHCOCH_3$	CH_3	15	6						

*Optimal dose is highest dose tested.

†Data of DR&D, DCT, NCI. Vehicle = saline.

TABLE 4.—Structure-activity relationships: fission N_4–9_a bond



NSC No. (supplier's code No.)	Substituents		Expt 2		Expt 3		Expt 5	
	X	R	Optimal dose (mg/kg)	ILS (%)	Optimal dose (mg/kg)	ILS (%)	Optimal dose (mg/kg)	ILS (%)
26980 Mitomycin C			5.3*	58	5.25*	77	3.5	29
134729 (K-37)	NH_2	$NHCH_2$	93.5*	14	187*	20		
134717 (K-1)	CH_3O	NH_2	7.0*	32			4.7†	10

*Optimal dose is highest dose tested.

†Optimal dose is lowest dose tested.

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Methanesulfonates: The Relationship of Structure to Antitumor Activity [1]

Joel S. Sandberg,[2] Harry B. Wood, Jr.,[3] Robert R. Engle,[3] John M. Venditti,[4] and Abraham Goldin [2,5]

Studies on the relationship of structure to antitumor activity of purine and pyrimidine nucleosides (1) and compounds related to folic acid (2) have been reported. In its chemotherapy program, the National Cancer Institute (NCI) continues to study the structure-activity relationships among different classes of antitumor agents. The present report is a study of methanesulfonates.

In an attempt to prepare drugs with an action resembling that of nitrogen mustards, Haddow and Timmis in 1951 (3) showed that the introduction of sulfonic acid ester groups conferred the property of biologic alkylation on the ethyl groups of diethylarylamines. One of a group of methanesulfonates thus synthesized, 1,4-dimethanesulfonyloxybutane (busulfan, Myleran; NSC-750; entry No. 90036) demonstrated a striking inhibitory effect on the growth of Walker rat carcinosarcoma 256 (4). The finding that busulfan selectivity depressed the myeloid series of hematopoietic cells, led to its use in myelogenous leukemia in man (5–7). Synthesis of new methanesulfonates in an attempt to increase antitumor activity has continued from this beginning (8). A large number of these compounds have been tested in the screening program of the Division of Cancer Treatment (DCT), NCI (9). In the current report, the Drug Research and Development data on methanesulfonates will be summarized and structure-activity relationships examined.

METHODS

The methods are those used in the screening program of DCT, NCI (10–12). Table 1 outlines the six in vivo systems and the one in vitro assay system. In the leukemia L1210 system, a 25% increase in the survival time of the treated mice as compared with controls is considered to indicate a significant chemotherapeutic effect.[6] In the assay systems utilizing Walker carcinosarcoma 256 (W-256), Adenocarcinoma 755 (CA-755), Sarcoma 180 (S-180), and Lewis lung carcinoma (LL), a 75% inhibition of local tumor growth as compared with controls was considered as indicative of activity. Seventy-five percent inhibition has been used to indicate activity in previous retrospective analyses (1,2,13).[7] The KB system is a tissue culture assay for cytotoxicity. A 50% inhibition of growth as reflected by inhibition of protein production at 1 μg/ml or less of a compound indicated significant biologic activity. The agents tested are listed in table A.

[1] Received Mar 24, 1971; accepted Aug 18, 1972.

[2] Drug Research and Development (DR&D), Division of Cancer Treatment (DCT), National Cancer Institute (NCI).

[3] Drug Development Branch, DR&D, DCT, NCI.

[4] Drug Evaluation Branch, DR&D, DCT, NCI.

[5] The authors wish to thank Mrs. Miriam Gang for her help with the calculations and Mrs. Linda Henry and Mrs. Sally Bernstein for secretarial assistance.

[6] In our primary screening against L1210, an increase in mean survival time (MST) ≥ 25% over controls is regarded as sufficient to warrant further testing of the material. In subsequent testing in which the theoretically optimal dose may be more nearly approximated, an increase in MST ≥ 50% is generally required for further development toward clinical trial.

[7] DCT, NCI criteria for "activity" against "solid" tumors have required a maximum inhibition of the local tumor of 58% of the control tumor weight and a therapeutic index (LD10/minimum effective dose required for 58% tumor inhibition) ≥ 2.0.

RESULTS

Table 2 summarizes the spectrum of antitumor activity of 277 methanesulfonates examined in this study. For each structural subclass, table 2 shows the number of materials that were active over the number of materials tested in each of the assays. NSC numbers of the active materials are also listed.

The experimental results for each compound in each structural subclass are summarized in table 3.

1. Alkyl and Cyclic Alkyl Methanesulfonates Without Nitrogen

There were 29 compounds in this series. Only one of the 25 tested against L1210, 2-fluoroethyl methanesulfonic acid ester (NSC-52142; entry No. 89989) showed activity (ILS = 45%). This compound was inactive against CA-755 and in the KB system and was not tested against W-256, S-180, or LL tumors. The two other halogenated derivatives, 2-chloroethyl methanesulfonate (NSC-18016; entry No. 89979) and 2-bromoethyl methanesulfonate (NSC-49551; entry No. 89986) were inactive against L1210. The chloro derivative (NSC-18016) was, however, active against CA-755 (TWI = 79%) and showed marginal activity (TWI = 70%) against W-256. Three of ten compounds tested against W-256 were active; methyl methanesulfonate (NSC-50256; entry No. 89988), 4-hydroxybutyl methanesulfonate (NSC-67176; entry No. 89990), and 2,3-dibromo-2-propen-1-ol methanesulfonate (NSC-106788; entry No. 89993). None of the compounds tested in the other assays showed activity. However, there are wide gaps in the experimental data. None of the cyclic alkyl methanesulfonates in this group showed significant in vivo or in vitro antitumor activity.

2. Aromatic Methanesulfonates Without Nitrogen

None of the 17 aromatic methanesulfonates without nitrogen showed antitumor activity. Sixteen of the compounds were tested and found inactive against L1210. The nine compounds tested against W-256, the four compounds tested against both CA-755 and S-180, and the one compound tested against KB cells were inactive.

3. Heterocyclic Methanesulfonates Without Nitrogen

Six of the heterocyclic methanesulfonates without nitrogen were tested and found inactive against L1210. None of the four compounds (NSC-19788 [entry No. 90023], NSC-68223 [entry No. 90024], NSC-73494 [entry No. 90025], NSC-97891 [entry No. 90026]) tested in vitro in the KB system were active. Only one compound, NSC-19788, was tested in other systems and it was inactive against CA-755 and S-180.

4. Steroid Methanesulfonates

Three of the four compounds in this category were tested against L1210 and were inactive. All four compounds were inactive against S-180 and only one of them (NSC-75339E; entry No. 90035) was tested in the KB system and was found to be inactive.

5. Two or More Methanesulfonates Without Nitrogen

There were 31 compounds in this category. The only one of the 15 tested against L1210 which was active (ILS = 31%) was 1,9-nonanediol dimethanesulfonate (nonane, NSC-3052; entry No. 90037), which has nine methylene groups separating the two methanesulfonates. It was also active against W-256 (TWI = 83%) and showed marginal activity against CA-755 (TWI = 74%) but was not active against S-180. Compounds with lesser numbers of methylene groups, including 1,2-ethyleneglycol dimethanesulfonate (NSC-17016; entry No. 90038) (two methylene groups), 1,3-propanediol dimethanesulfonate (NSC-17017; entry No. 90039) (three methylene groups), 1,4-butanediol dimethanesulfonate (busulfan, NSC-750; entry No. 90036) (four methylene groups), and 1,5-pentanediol dimethanesulfonate (NSC-17019; entry No. 90040) (five methylene groups), were not active against L1210. The compounds with two and three methylene groups separating the methanesulfonyl groups (NSC-17016 and NSC-17017) were not tested against W-256 and were inactive against S-180. However, NSC-17017 produced a 75% TWI against CA-755. In addi-

tion to NSC-3052 (nonane), two other compounds in this series which were tested in the W-256 system, namely, busulfan (NSC-750) and 1,5-pentanediol dimethanesulfonate (NSC-17019), did demonstrate activity. Busulfan did not show significant antitumor activity in the other systems; however, it has not been tested against the Lewis lung tumor. It may be noted that 1,4-butanediol di(chloromethylsulfonate) (NSC-106308; entry No. 90059), where a chlorine has been substituted for a hydrogen on each of the methanesulfonyl groups of busulfan, retained activity against W-256. This drug has not been tested against L1210. The 2,5-hexanediol dimethanesulfonate (NSC-23890; entry No. 90041), with methyl groups replacing hydrogen atoms on the butane moiety of busulfan, was not active in any of the systems in which it was tested, including W-256. None of 19 compounds tested passed the KB test, although 2-butyne-1,4-diol dimethanesulfonate (NSC-75141; entry No. 90049) had suggestive activity (ED50 = 1.3 μg/ml).

6. Three- and Four-Carbon Sugar Methanesulfonates Without Nitrogen

Only six of the 22 compounds in this category were tested for in vivo activity and only three of these were tested in the L1210 system. The L-threitol-1,4-dimethanesulfonate (NSC-39069; entry No. 90068) showed activity in the W-256 and CA-755 systems and borderline L1210 activity, all at very high doses. The meso isomer, erythritol 1,4-dimethanesulfonate (NSC-39070; entry No. 90069), showed no in vivo antitumor activity but it was not tested in doses as high as proved active with NSC-39069. NSC-39070 was not tested in the W-256 system. The D isomer (NSC-39068; entry No. 90067) was inactive against LL at a high dose but was not tested against L1210 or the other tumor systems. DL-Threitol 1,4-dimethanesulfonate (NSC-98767; entry No. 90088) gave a 59% TWI against the W-256 tumor but was tested at less than one fifth of the dose that proved active with NSC-39069. 2,3-*O*-isopropylidene L-threitol dimethanesulfonate (NSC-60499; entry No. 90070) was not active against L1210, CA-755, or S-180. L-1,2,4-Butanetriol 1,4-dimethanesulfonate (NSC-82399; entry No. 90084) was active against CA-755 at the one dose tested but was not tested in the other in vivo systems. None of the compounds met the requirement for activity in the KB system.

7. Five-, Six-, and Seven-Carbon Sugar Methanesulfonates Without Nitrogen

This group, containing 59 compounds, is the largest in the collection. None of the 36 compounds tested against L1210 showed activity. D-Mannitol 1,6-dimethanesulfonate (mannitol myleran) (NSC-37538; entry No. 90101) was active against W-256 at a high dose but was not active against the other in vivo tumors or against KB cells in culture. None of the seven other compounds in this category which were tested against W-256 showed activity. The other mannitol derivatives, galactitols, sorbitols, glucitols, and iditols had no in vivo tumor activity. None of the 36 compounds tested in the KB tissue culture system were active.

8. Mono Methanesulfonates With Nitrogen

The group of "one-armed" methanesulfonates contains seven compounds. The four compounds tested against L1210 showed no activity. 2-(*p*-Nitroanalino)ethyl methanesulfonate (NSC-100773; entry No. 90152), with an ILS of 19% in the L1210 system and an ED50 of 2.4 μg/ml against KB cells, showed suggestive activity and might be worthy of further testing. There was little testing in the other in vivo systems.

9. Dimethanesulfonates With Nitrogen

Three of the six compounds in this category were tested against L1210 and were active. NSC-102627 (entry No. 90159) differs from NSC-84641 (entry No. 90158) in that the former has a hydrogen atom and the latter a methyl group attached to the amino nitrogen. Both compounds show extensive anti-L1210 activity at about the same dose range. Decreasing the number of methylene groups separating the methanesulfonyl groups from the amino nitrogen from three (in NSC-102627) to two produced a compound (NSC-115485; entry No. 90160) which was less active against L1210 than NSC-102627. The other three compounds in this category were not tested in vivo and were inactive in the KB system.

10. *N*-Aryl-Substituted Dimethanesulfonates With Nitrogen

There were 27 compounds in this category. The simplest compound, NSC-71035 (entry No. 90166), was inactive against L1210 but active against W-256. However, of the various *N*-aryl-substituted derivatives in this category, 15 of 26 tested against L1210 showed significant activity. The highest rating achieved was for NSC-104967 (entry No. 90187), with an acetamido moiety in the meta position (ILS = 68%). Compounds with nitro (NSC-100774; entry No. 90171), amino (NSC-102469; entry No. 90178), chloro (NSC-101671; entry No. 90172), and fluoro (NSC-103363; entry No. 90180) substituents in the meta position of the phenyl ring were decreasingly less effective than NSC-104967.

NSC-100774 (entry No. 90171) with a nitro group in the meta position showed greater anti-L1210 activity than NSC-101673 (entry No. 90174) with the nitro in the para position. With the nitro group in the para position, further addition of a fluorine, chlorine, or a trifluoromethyl group ortho to the nitro substituent, as in NSC-104962 (entry No. 90183), NSC-104965 (entry No. 90186), and NSC-104963 (entry No. 90184), did not essentially increase anti-L1210 activity. The benzene diazonium derivative (NSC-82361; entry No. 90170) and the coumarin derivative (NSC-72151; entry No. 90167) gave an ILS of 57% and 48% respectively against L1210.

Sixteen of the 18 compounds tested against W-256 were active. Various substitutions on the phenyl ring did not decrease the activity against W-256 and, in fact, may have actually increased it in a number of cases. One exception would appear to be NSC-103362 (entry No. 90179) where there was a decrease in activity. However, this drug was tested at only one dose level. Also, NSC-104963 (entry No. 90184) was tested at only one dose level and was toxic.

None of the compounds were tested against CA-755, S-180, or LL tumors.

Four of 13 compounds showed significant activity in the KB system.

Two of these (NSC-79423 [entry No. 90168] and NSC-103961 [entry No. 90181]) were also active against L1210 and three (NSC-79423 [entry No. 90168], NSC-103961 [entry No. 90181], and NSC-104964 [entry No. 90185]) were active against W-256.

11. Piperazine Dimethanesulfonates

1,4-Diglycoloyl piperazine dimethanesulfonate (NSC-53577; entry No. 90189) showed no L1210, CA-755, or S-180 activity. It was not tested against W-256, LL, or KB cells. An increase in the number of carbon atoms separating the methanesulfonyl moiety and the nitrogen from two, as in NSC-53577, to three, as in NSC-47774 (entry No. 90188), resulted in a compound which was active against L1210, W-256, and CA-755. Further, methylation of the hydracryloyl moiety with one methyl group, as in NSC-57845 (entry No. 90190), or two methyl groups, as in NSC-61152 (entry No. 90192), resulted in a loss of anti-L1210 and anti-CA-755 activity, but no data were available for W-256. However, methylation of the piperazine moiety, as in 1,4-dihydracryloyl-*trans*-2,5-dimethyl piperazine dimethanesulfonate (NSC-61147; entry No. 90191), did not diminish the anti-L1210, anti-W-256, or anti-CA-755 activity. None of the five piperazine dimethanesulfonates in this category were active against S-180. Only one of the five compounds was tested against LL where it was inactive, and there was no data for the KB system.

12. Diamine Dimethanesulfonates

The hydracrylamide dimethanesulfonate in which the amino groups are separated by one methylene group (NSC-57844; entry No. 90200) yielded a 43% ILS against L1210 and was also active against the W-256 and CA-755 tumors. The hydracrylamide dimethanesulfonates in which the amino groups are separated by more than one methylene group (two CH_2, NSC-53582 [entry No. 90194]; three CH_2, NSC-55109 [entry No. 90196]; four CH_2, NSC-55110 [entry No. 90197]; five CH_2, NSC-55111 [entry No. 90198]; and six CH_2, NSC-55112 [entry No. 90199]) were not active against L1210, although NSC-53582 was active against KB cells in tissue culture. However, NSC-61151 (entry No. 90203), with a methyl-substituted ethylene group separating the amino groups, produced a 41% ILS against L1210.

The two glycolamide dimethanesulfonates tested, NSC-24901 (entry No. 90193) and NSC-58825 (entry No. 90202), in which the amino groups were separated by two and three methylene groups respectively, were both active against L1210. The hydracrylamide and glycolamide dimethanesulfonates tested were active against W-256, except NSC-55112 (entry No. 90199), which was tested at only one dose. Similarly, the hydracrylamide and glycolamide dimethanesulfonates tested were active against CA-755, except NSC-58825 and NSC-55112, which were tested at only one dose, and NSC-61151 (entry No. 90203), which yielded a 68% TWI. None of the compounds in this category that were tested against S-180 showed activity in this tumor system. The one compound tested against LL was inactive.

The compounds in this category which showed the greatest anti-L1210 activity were NSC-106625 (entry No. 90206) (ILS = 63%) and NSC-122402 (entry No. 90207) (ILS = 130%), both of which are amines rather than amides. NSC-122402 is a four-carbon sugar dimethanesulfonate, while NSC-106625 has five methylene groups separating the amino groups.

13. Aminobutanediols Methanesulfonates

The 16 compounds in this category were tested only in the in vitro KB system. All were found to be inactive.

14. Nucleoside Methanesulfonates

Of the 14 compounds in this category, six were tested against L1210 and were inactive. Testing in the other in vivo tumor systems was limited. None of the compounds was active against KB cells in culture.

15. Miscellaneous Compounds Containing Methanesulfonates

Of the 16 compounds in this miscellaneous group of methanesulfonates, 13 were tested against L1210 and were inactive. Where tested, no activity was noted in any of the other in vivo systems or against KB cells in culture.

DISCUSSION AND CONCLUSIONS

Two hundred and seventy-seven compounds containing the methanesulfonate moiety were tested for antitumor activity in the DR&D screens. A summary listing of the spectrum of activity is presented in table 2, and pertinent structure-activity relationships pertaining to the active compounds are summarized in tables 4–11.

Although it is not an absolute requirement, the presence of nitrogen appears to increase the potential for antitumor activity of the methanesulfonates. Of the two broad categories of methanesulfonates, the compounds containing nitrogen (table 2, groups 8–15) demonstrated a greater percentage of actives than the compounds without nitrogen (table 2, groups 1–7) in the L1210, W-256, and CA-755 systems. For the compounds with nitrogen, the percentages of active compounds were as follows: L1210, 26/69 (37.7%); W-256, 23/37 (62.2%); CA-755, 9/21 (42.9%). The percentages for compounds without nitrogen were as follows: L1210, 3/104 (2.9%); W-256, 9/37 (24.3%); CA-755, 4/43 (9.1%). Also, in the L1210 system, the most extensive increases in survival time were observed with nitrogen-containing methanesulfonates. In the KB tissue culture system there were five of 61 active nitrogen-containing methanesulfonates and no active (0 of 88) non-nitrogen-containing methanesulfonates.

The first seven categories of agents were those methanesulfonates without nitrogen. These compounds represented a wide range of structures including alkyl, cyclic, aromatic, heterocyclic, and steroid methanesulfonates without nitrogen, two or more methanesulfonates without nitrogen, and three-, four-, five-, and six-carbon sugar methanesulfonates without nitrogen. There were only three compounds in these groups that showed activity in the L1210 system: 2-fluoromethyl methanesulfonate (NSC-52142 [entry No. 89989]; table 2, group 1; table 4), 1,9-nonanediol, dimethanesulfonate (NSC-3052 [entry No. 90037]; table 2, group 5; table 5), and L-threitol, 1,4-dimethanesulfonate (NSC-39069 [entry No. 90068]; table 2, group 6; table 6). All three of these compounds demonstrated only borderline activity, increasing survival time 45%, 31%, and 32% respectively.

Data on structural analogs related to 2-fluoroethyl methanesulfonate (NSC-52142; entry No. 89989) are summarized in table 4. Although 2-fluoroethyl methanesulfonate was active against leukemia L1210, a wide variety of alkyl (and cyclic) derivatives were inactive, including 2-chloroethyl and 2-bromoethyl methanesulfonates. Indicative of differences in structural requirements for activity against different tumors, however, is the finding that three other derivatives, the methyl (NSC-50256; entry No. 89988), 4-hydroxybutyl (NSC-67176; entry No. 89990) and 2,3-dibromo-2-propan-1-ol (NSC-106788; entry No. 89993) methanesulfonates, rated as inactive against L1210, were active against W-256. Also, 2-chloroethyl methanesulfonate, although inactive against L1210, was active against CA-755.

1,9-Nonanediol dimethanesulfonate (NSC-3052; entry No. 90037) was active not only against leukemia L1210 but also against W-256 (table 2, group 5; table 5). Busulfan (Myleran; NSC-750; entry No. 90036), the methanesulfonate used clinically (4–7), was inactive against leukemia L1210 but initially aroused interest because of its activity against the W-256 tumor (2). In similarity to busulfan, 1,5-pentanediol, dimethanesulfonate (NSC-17019; entry No. 90040) was inactive against leukemia L1210 but active against W-256. These results, plus the observation that the trimethylene ester of methanesulfonic acid (NSC-17017; entry No. 90039) was inactive in the L1210 system but active in the CA-755 system, again indicate that there is no necessary relationship between structure and extent of uniformity of response in the various tumor screens.

Compounds related to the four-carbon sugar L-threitol, 1,4-dimethanesulfonate (NSC-39069; entry No. 90068; table 2, group 6) are listed in table 6. It is of interest that the L-threitol derivative NSC-39069 was active at high dosage not only against leukemia L1210 but also against W-256 and CA-755. The compound differs in its activity from busulfan (NSC-750; entry No. 90036) since busulfan, as indicated above, has not demonstrated activity against leukemia L1210. It may be noted that DL-threitol, 1,4-dimethanesulfonate (NSC-98767; entry No. 90088) showed reduced activity against W-256, but it is possible that the dose given was too low. The activity of L-1,2,4-butanetriol, 1,4-dimethanesulfonate (NSC-82399; entry No. 90084) against CA-755 suggests that this compound is worthy of testing against leukemia L1210 and W-256. It is of interest to note that, where tested, none of the five-carbon sugar methanesulfonates were active.

In similarity to busulfan, the six-carbon sugar methanesulfonates without nitrogen, mannitol-1,6-dimethanesulfonate (mannitol myleran) (NSC-37538 [entry No. 90101], table 2, group 7; table 7) was inactive against leukemia L1210 but highly effective against W-256 and other experimental tumor systems (14,15). It is effective in human chronic myelogenous leukemia (16). It is evident that additional data for compounds such as NSC-117359 (entry No. 90144), NSC-122801 (entry No. 90145), and NSC-80604 (entry No. 90120) are necessary for further analysis.

The four "one-armed" methanesulfonates containing nitrogen (table 2, group 8) tested against L1210 were inactive, and further testing would be required in the other screening systems. Whether this class of compounds resembles the "one-armed" methanesulfonates without nitrogen in evidencing little activity in the L1210 system but a higher incidence of activity in the W-256 system remains to be determined.

In contrast, 26 dimethanesulfonates containing nitrogen (table 2, groups 9–12; tables 8–11) were active in the L1210 system. NSC-102627 (entry No. 90159) and NSC-84641 (entry No. 90158), with three methylene groups separating the single amino group and each of the methanesulfonyl groups, showed extensive anti-L1210 activity. The activity of these two compounds was three to four times greater than for the compound with two methylene groups, NSC-115485 (entry No. 90160) (table 2, group 9; table 8). NSC-102627 and NSC-84641 are methanesulfonates of current interest (17,18). These observations suggest an interest in exploration of analogs of this type with increased numbers of methylene groups. As indicated above, even nonane (NSC-3052; entry No. 90037), the non-nitrogen dimethanesulfonate with nine methylene groups, exhibited moderate activity against leukemia L1210.

The *N*-aryl-substituted dimethanesulfonates with nitrogen (table 2, group 10; table 9), constituted an L1210-active class of compounds. Ten of the compounds with a single substituent on the phenyl ring were active against L1210 leukemia, of which NSC-104967 (entry No. 90187) with an acetamido substituent in the meta position showed the highest activity (ILS = 68%). Other derivatives, including those with nitro, nitroso, amino, chloro, fluoro, trifluoromethyl, and more complex substituents on the phenyl ring, showed lesser L1210 activity. It may be noted that NSC-79423 (entry No. 90168) has demonstrated activity in a variety of other tumor systems. Five of the compounds with substituents in two positions on the phenyl ring were active against L1210 leukemia, but the increases in survival time were not extensive. All of the drugs in group 10 that were active against L1210 have two ethyl methanesulfonyl groups attached to one amino nitrogen, and when tested they were active against W-256. It is interesting to note that additional structures which were not active against L1210 leukemia, including the unsubstituted phenyl derivative NSC-71035 (entry No. 90166), were active against W-256.

Two of the piperazine derivatives, NSC-47774 (entry No. 90188) and NSC-61147 (entry No. 90191) were active against L1210, W-256, and CA-755. They have two unsubstituted methylene groups and a carbonyl group which is attached to the nitrogen separating the nitrogen and methanesulfonyl groups (table 2, group 11; table 10). The relatively broad spectrum of activity for these congeners suggests additional synthesis of piperazine dimethanesulfonate derivatives.

Among the diamine dimethanesulfonates, the two glycolamide derivatives (NSC-24901 [entry No. 90193] and NSC-58825 [entry No. 90202]) and two of the hydracrylamide derivatives (NSC-57844 [entry No. 90200] and NSC-61151 [entry No. 90203]) were active against L1210 leukemia (table 2, group 12; table 11). One of the glycolamides (NSC-24901) was also active against W-256 and CA-755. In the hydracrylamide series, NSC-57844 and NSC-61151 were active not only against L1210 leukemia but also against W-256, and the former was also active against CA-755. For the hydracrylamides, an increase in the number of methylene groups separating the two nitrogens resulted in a rapid loss of anti-L1210 activity, with greater retention of activity against W-256 (in at least one instance) and against CA-755. Activity against CA-755 was finally lost with NSC-55112 (entry No. 90199), where six methylene groups separated the two nitrogens. Both of the compounds in this group without carbonyl groups adjacent to the nitrogens (NSC-122402 [entry No. 90207] and NSC-106625 [entry No. 90206]) have demonstrated activity. The diamine sugar alcohol NSC-122402 (R-74)[5] has shown marked anti-L1210 activity (19), and NSC-106625, with four methylene groups separating the amino groups, was active against both L1210 and W-256. NSC-106625 is also of current interest (17,18).

The CA-755 system has been effective for predicting clinical antitumor activity of purine antagonists (20,21). In total, 14 compounds were found to be active against CA–755. Four of these were compounds without nitrogen: 2-chloroethyl methanesulfonate (NSC-18016 [entry No. 89979]; group 1), 1,3-propanediol dimethanesulfonate (NSC-17017 [entry No. 90039]; group 5), and NSC-39069 [entry No. 90068] and NSC-82399 [entry No. 90084], two four-carbon sugar dimethanesulfonates. Of these four compounds, NSC-18016 has been reported to have striking activity against Lymphoma 8 (22). The two piperazine dimethanesulfonates found active against CA-755 (NSC-47774 [entry No. 90188] and NSC-61147 [entry No. 90191]; table 2, group 11; table 10) were the same piperazines found active in L1210 and W-256. The eight remaining compounds active against CA-755 were hydracrylamide and glycolamide dimethanesulfonates. Two of the three compounds in this category not active against CA-755 were tested at only one dose.

Where tested, there were no compounds in the entire group of methanesulfonates that showed activity against the S-180 tumor. It may be noted that following an extensive retrospective analysis of the predictability value of screens for the clinic (13,23), more emphasis has been placed on the L1210 and W-256 systems than the S-180 system.

[5] Synthesized by T. Horvath et al and subjected to limited clinical trials by C. Sellei. Personal communication (*see* reference 19).

There were no compounds containing methanesulfonate that showed activity against the LL tumor. However, only a small fraction of the total number of compounds was tested in this system. Several compounds that were active in the L1210, W-256, and CA-755 systems were tested in the LL system and found to be inactive.

The nucleoside methanesulfonates (table 2, group 14) received only limited testing, and any antitumor potential for this type of structure remains to be explored.

The subject of biologic alkylating agents has been reviewed extensively (24–28). One of the major deterrents to further experimental work with methanesulfonates is the view that "they are just another group of alkylating agents." Although methanesulfonates are members of the alkylating agent class, there are differences in the consequences of their action as compared to the bis(2-chloroethyl) amines (29). For example, the divergent effects of chlorambucil and busulfan have been demonstrated experimentally (30,31) and clinically against chronic lymphocytic and granulocytic leukemia (32,33). The screening data presented in this study show that there are broad differences among the methanesulfonates themselves regarding antitumor activity. The wide range of structural analogs showing activity in the L1210 and W-256 systems and the available data suggesting activity modification as the resultant of structural alterations suggest that the methanesulfonates may be further exploited for the synthesis and evaluation of new compounds with improved antitumor effectiveness.

TABLE A.—List of agents tested

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
750	90036	55-98-1	1,4-Butanediol, dimethanesulfonate	$O_6S_2C_6H_{14}$
3052	90037	4248-77-5	1,9-Nonanediol, dimethanesulfonate	$O_6S_2C_{11}H_{24}$
3718	89977	75-75-2	Methanesulfonic acid	$O_3SC\ H_4$
14162	90089	—	D-Glucofuranose, 1,2:5,6-di-*O*-isopropylidene-, methanesulfonate	$O_6SC_{13}H_{22}$
17016	90038	4672-49-5	Methanesulfonic acid, ethylene ester	$O_6S_2C_4H_{10}$
17017	90039	15886-84-7	Methanesulfonic acid, trimethylene ester	$O_6S_2C_5H_{12}$
17018	89978	—	Methanesulfonic acid, 2-phenoxyethyl ester	$O_4SC_9H_{12}$
17019	90040	2374-22-3	1,5-Pentanediol, dimethanesulfonate	$O_6S_2C_7H_{16}$
18016	89979	3570-58-9	Ethanol, 2-chloro-, methanesulfonate	$O_3SClC_3H_7$
19784	90006	5444-15-5	Methanesulfonic acid, 2,5-diiodo-4-nitrophenyl ester (phenol, 2,5-diiodo-4-nitro-, methanesulfonate)	$NO_5SI_2C_7H_5$
19785	90007	7155-37-5	Methanesulfonic acid, 2,4-dinitrophenyl ester (phenol, 2-4-dinitro-, methanesulfonate)	$N_2O_7SC_7H_6$
19788	90023	5443-45-8	4*H*-pyran-4-one, 5-hydroxy-2-(hydroxymethyl)-, dimethanesulfonate	$O_8S_2C_8H_{10}$
20669	89980	6968-20-3	Methanesulfonic acid, pentyl ester	$O_3SC_6H_{14}$
23890	90041	55-93-6	2,5-Hexanediol, dimethanesulfonate	$O_6S_2C_8H_{18}$
24820	90161	—	Benzaldehyde, *p*-[bis-(2-hydroxyethyl)amino]-, dimethanesulfonate	$NO_7S_2C_{13}H_{19}$
24897	89981	3586-50-3	Glycolic acid, methanesulfonate	$O_5SC_3H_6$
24899	90042	5457-47-6	Glycolic acid, ethylene ester, dimethanesulfonate	$O_{10}S_2C_6H_{14}$
24900	90043	—	Glycolic acid, 2-hydroxyethyl ester, dimethanesulfonate	$O_8S_2C_5H_{12}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
24901	90193	—	Glycolamide, *N,N'*-ethylene-bis-, dimethanesulfonate	$N_2O_8S_2C_6H_{16}$
26358	89982	—	Methanesulfonic acid, 2-cyanoethyl ester	$NO_3SC_4H_7$
26805	89983	62-50-0	Methanesulfonic acid, ethyl ester	$O_3SC_3H_8$
27401	90162	—	Phosphonic acid, (*p*-[bis-(2-hydroxyethyl)-amino]benzyl)-, diethyl ester, dimethanesulfonate	$NO_8PS_2C_{17}H_{30}$
29838	90008	—	Hydrazine, 1-(dichloroacetyl)-2-(*p*-hydroxybenzoyl)-, methanesulfonate	$N_2O_5SC_{12}C_{10}H_{10}$
31720	90090	7511-62-8	Methanesulfonic acid, tetraester with pentaerythritol	$O_{12}S_4C_9H_{20}$
33261	90091	—	D-Glucofuranose, 1,2-*O*-isopropylidene-, trimethanesulfonate	$O_{11}S_3C_{12}H_{22}$
33267	90092	—	D-Glucofuranoside, methyl, 3,5,6-tribenzoate 2-methanesulfonate	$O_{11}SC_{29}H_{28}$
33694	90093	—	D-Sorbitol, 1,4:3,6-dianhydro-, dimethanesulfonate	$O_8S_2C_8H_{14}$
33695	90094	24808-23-9	D-Mannitol, 1,4:3,6-dianhydro-, dimethanesulfonate	$O_8S_2C_8H_{14}$
33696	90095	—	β-D-Mannopyranose, 1,6-anhydro-2,3-*O*-isopropylidene-, methanesulfonate	$O_7SC_{10}H_{16}$
33697	90096	—	D-Mannitol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-, methanesulfonate	$O_6SIC_7H_{11}$
33698	90097	—	D-Sorbitol, 1,4:3,6-dianhydro-2(or 5)-deoxy-2(or 5)-iodo-, methanesulfonate	$O_6SIC_7H_{11}$
33699	90098	—	D-Mannitol, 1,6-dibenzoate 2,3,4,5-tetramethanesulfonate	$O_{16}S_4C_{24}H_{30}$
34439	90099	—	Sucrose, tetraacetate tetramethanesulfonate	$O_{23}S_4C_{24}H_{38}$
34532	90100	—	Sucrose, tetramethanesulfonate	$O_{19}S_4C_{16}H_{30}$
36060	89984	1912-32-9	Methanesulfonic acid, butyl ester	$O_3SC_5H_{12}$
37538	90101	1187-00-4	Mannitol, 1,6-dimethanesulfonate, D-	$O_{10}S_2C_8H_{18}$
39068	90067	1947-62-2	D-Threitol, 1,4-bis(methanesulfonate)	$O_6S_2C_6H_{14}$
39069	90068	299-75-2	L-Threitol, 1,4-dimethanesulfonate	$O_6S_2C_6H_{14}$
39070	90069	2297-56-5	Erythritol, 1,4-bis(methanesulfonate)	$O_6S_2C_6H_{14}$
39114	90102	—	α-D-Glucopyranoside, methyl, 2,6-bis(methanesulfonate)	$O_{10}S_2C_9H_{18}$
39268	90103	—	β-D-Arabinopyranoside, benzyl, 2-methanesulfonate	$O_7SC_{12}H_{16}$
40485	90009	6317-27-7	Methanesulfonic acid, *p*-chlorophenyl ester	$O_3SClC_7H_7$
44342	90148	6973-24-6	Carbamic acid, (2-hydroxyethyl)-, methyl ester, methanesulfonate	$NO_6SC_5H_{11}$
47774	90188	2608-24-4	Piperazine, 1,4-dihydracryloyl-, dimethanesulfonate; piposulfan	$N_2O_8S_2C_{12}H_{22}$
49507	89985	4239-16-1	Methanesulfonic acid, 3-chloropropyl ester	$O_3SClC_4H_9$
49551	89986	4239-10-5	Ethanol, 2-bromo-, methanesulfonate	$O_3SBrC_3H_7$
49872	89987	1912-31-8	Methanesulfonic acid, propyl ester	$O_3SC_4H_{10}$
50256	89988	66-27-3	Methanesulfonic acid, methyl ester	$O_3SC_2H_6$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
52142	89989	461-31-4	Methanesulfonic acid, 2-fluoroethyl ester	$O_3SFC_3H_7$
52400	90104	6945-62-6	α-D-Altropyranoside, methyl 4,6-*O*-benzylidene-3-deoxy-3[(dithiocarboxy)amino]-, methyl ester, methanesulfonate	$NO_7S_3C_{17}H_{23}$
53577	90189	—	Piperazine, 1,4-diglycoloyl-, dimethanesulfonate	$N_2O_8S_2C_{10}H_{18}$
53581	90238	—	Piperidine, 4,4′-ethylenebis[1-hydracryloyl-, dimethanesulfonate	$N_2O_8S_2C_{20}H_{36}$
53582	90194	—	Hydracrylamide, *N,N′*-ethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{10}H_{20}$
54012	90163	4171-09-9	Benzaldehyde, *p*-[bis(2-hydroxyethyl)amino]-, purin-6-ylhydrazone, dimethanesulfonate ester, hydrochloride	$N_7O_6S_2C_{18}H_{23} \cdot HCl$
54688	90044	2434-87-9	*trans*-5-Norbornene-2,3-dimethanol, dimethanesulfonate	$O_6S_2C_{11}H_{18}$
55104	90195	—	Hydracrylamide, *N,N′*-*p*-phenylenebis-, dimethanesulfonate	$N_2O_8S_2C_{14}H_{20}$
55109	90196	—	Hydracrylamide, *N,N′*-trimethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{11}H_{22}$
55110	90197	—	Hydracrylamide, *N,N′*-tetramethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{12}H_{24}$
55111	90198	—	Hydracrylamide, *N,N′*-pentamethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{13}H_{26}$
55112	90199	—	Hydracrylamide, *N,N′*-hexamethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{14}H_{28}$
57844	90200	—	Hydracrylamide, *N,N′*-methylenebis-, dimethanesulfonate	$N_2O_8S_2C_9H_{18}$
57845	90190	—	Piperazine, 1,4-bis(2-methylhydracryloyl)-, dimethanesulfonate	$N_2O_8S_2C_{14}H_{26}$
57847	90239	—	*s*-Triazine, 1,3,5-trihydracryloylhexahydro-, trimethanesulfonate	$N_3O_{15}S_3C_{18}H_{27}$
58805	90201	—	Acetamide, *N,N′*-tetramethylenebis[2-hydroxy-, dimethanesulfonate	$N_2O_8S_2C_{10}H_{20}$
58819	90045	—	2-Propanone, 1,3-dihydroxy-, dimethanesulfonate	$O_7S_2C_5H_{10}$
58825	90202	27687-75-8	Glycolamide, *N,N′*-trimethylenebis-, dimethanesulfonate	$N_2O_8S_2C_9H_{18}$
59640	90164	—	Benzoic acid, *p*-[bis(2-hydroxyethyl)amino]-, dimethanesulfonate (ester)	$NO_8S_2C_{13}H_{19}$
59643	90165	—	Benzoic acid, *p*-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate (ester)	$NO_8S_2C_{15}H_{23}$
60499	90070	—	L-Threitol, 2,3-*O*-isopropylidene-, dimethanesulfonate	$O_8S_2C_9H_{18}$
61147	90191	—	Piperazine, 1,4-dihydracryloyl-*trans*-2,5-dimethyl-, dimethanesulfonate	$N_2O_8S_2C_{14}H_{26}$
61151	90203	—	Hydracrylamide, *N,N′*-propylenebis-, dimethanesulfonate	$N_2O_8S_2C_{11}H_{22}$
61152	90192	—	Piperazine, 1,4-bis(2,2-dimethylhydracryloyl)-, dimethanesulfonate	$N_2O_8S_2C_{16}H_{30}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
61154	90204	23256-07-7	Hydracrylamide, *N,N'*-(2-methyltrimethylene)bis-, dimethanesulfonate	$N_2O_6S_2C_{12}H_{24}$
62570	90240	—	5-Pyrimidinemethanol, 2,4-dichloro-6-methyl-, methanesulfonate	$N_2O_3SCl_2C_7H_8$
62627	90224	—	Guanosine, 5'-methanesulfonate	$N_5O_7SC_{11}H_{15}$
62796	90105	—	D-Ribose, 2-deoxy-, 5-methanesulfonate	$O_6SC_6H_{12}$
62797	90106	—	β-D-Ribofuranoside, methyl 2-deoxy-, 5-methanesulfonate	$O_6SC_7H_{14}$
62798	90107	—	β-D-Ribofuranoside, methyl 2-deoxy-, dimethanesulfonate	$O_8S_2C_8H_{16}$
62799	90108	—	β-D-Ribofuranoside, benzyl 2-deoxy-, 5-methanesulfonate	$O_6SC_{13}H_{18}$
63325	90071	—	L-Threitol, 2,3-*O*-phenethylidene-, dimethanesulfonate	$O_8S_2C_{14}H_{20}$
63379	90072	—	Erythritol, 2,3-*O*-cyclohexylidene-, dimethanesulfonate	$O_8S_2C_{12}H_{22}$
65402	90073	—	D-Threitol, 2,3-*O*-(2,2,2-trichloroethylidene)-, dimethanesulfonate	$O_8S_2Cl_3C_8H_{13}$
65403	90074	—	Erythritol, 2,3-*O*-(2,2,2-trichloroethylidene)-, dimethanesulfonate	$O_8S_2Cl_3C_8H_{13}$
66343	90075	—	L-Threitol, 2,3-*O*-ethylidene-, dimethanesulfonate	$O_8S_2C_6H_{14}$
66344	90076	—	D-Threitol, 2,3-*O*-ethylidene-, dimethanesulfonate	$O_8S_2C_6H_{14}$
66345	90077	—	Erythritol, 2,3-*O*-ethylidene-, dimethanesulfonate	$O_8S_2C_6H_{14}$
67128	90078	—	L-Threitol, 2,3-cyclic carbonate, dimethanesulfonate	$O_9S_2C_7H_{12}$
67129	90079	—	L-Threitol, 1,4-dimethanesulfonate cyclic sulfite	$O_8S_3C_6H_{12}$
67130	90080	—	L-Threitol, 2,3-bis(ethyl carbonate) 1,4-dimethanesulfonate	$O_{12}S_2C_{12}H_{22}$
67176	89990	—	Methanesulfonic acid, 4-hydroxybutyl ester	$O_4SC_5H_{12}$
67657E	90032	3752-56-5	5β-Cholane-3α,24-diol, dimethanesulfonate	$O_6S_2C_{26}H_{46}$
67658E	90033	—	5β-Cholane-3α,12α-diol, dimethanesulfonate	$O_6S_2C_{26}H_{46}$
67659E	90034	—	5β-Cholane-12α,24-diol, dimethanesulfonate	$O_6S_2C_{26}H_{46}$
68223	90024	—	4*H*-pyran-4-one, 5-hydroxy-2-(hydroxymethyl)-, 2-acetate, 5-methanesulfonate	$O_7SC_9H_{10}$
69435	90109	10469-70-2	α-D-Galactopyranoside, methyl, 4-methanesulfonate	$O_8SC_7H_{14}$
69567	90241	—	Flavone, *O*-(methylsulfonyl)oxime	$NO_4SC_{16}H_{13}$
70310	90149	—	L-Threitol, 1-(butylamino)-1-deoxy-2,3-*O*-methylene-, methanesulfonate, hydrochloride (1,3-dioxolane-4-methanol, 5-[(butylamino)methyl]-, methanesulfonate, hydrochloride)	$NO_6SC_{12}H_{25} \cdot HCl$
71035	90166	—	Ethanol, 2,2'-(phenylimino)-di-, dimethanesulfonate, hydrochloride	$NO_6S_2C_{12}H_{19} \cdot HCl$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
71088	90155	18352-53-9	Cinnamic acid, β-[bis(2-hydroxyethyl)-amino]-, ethyl ester, dimethanesulfonate	$NO_8S_2C_{17}H_{25}$
72151	90167	14415-46-4	Coumarin, 6-[[*p*-[bis(2-hydroxyethyl)-amino]benzylidene]amino]-, dimethanesulfonate (ester)	$N_2O_8S_2C_{22}H_{24}$
72392	90110	—	D-*glycero*-D-*gluco*-Heptitol, 1,3:2,3:5,7-tri-*O*-benzylidene-, methanesulfonate	$O_8SC_{29}H_{30}$
72473	90081	—	L-Threitol, 2,3-*O*-(2,2,2-trifluoroethylidene)-, dimethanesulfonate	$O_6S_2FC_8H_{13}$
72559	90111	4137-34-2	α-D-Galactopyranoside, methyl, 2,3,6-tribenzoate 4-methanesulfonate	$O_{11}SC_{35}H_{32}$
72602	90156	—	Cinnamic acid, β-[bis(2-hydroxyethyl)amino]-*p*-nitro-, methyl ester, dimethanesulfonate	$N_2O_{10}S_2C_{16}H_{22}$
72603	90157	18352-54-0	Ethanol, 2,2′-(*p*-nitrostyrylimino)di-, dimethanesulfonate	$N_2O_8S_2C_{14}H_{20}$
73269	90112	7254-24-2	α-D-Arabinofuranoside, methyl 3-deoxy-3-[(dithiocarboxy)amino]-, methyl ester, 2-methanesulfonate 5-(methyl carbonate)	$NO_9S_3C_{11}H_{19}$
73494	90025	—	1-Benzothiepin-5-ol, 2,3,4,5-tetrahydro-, 1,1-dioxide, methanesulfonate	$O_4S_2C_{11}H_{14}$
74885	90046	—	1,3-Propanediol, 2-methyl-2-(2,3,5,6-tetramethylbenzyl)-, dimethanesulfonate	$O_6S_2C_{17}H_{28}$
74902	90047	—	1,3-Propanediol, 2-(*o*-methyl-α-phenylbenzyl)-, dimethanesulfonate	$O_6S_2C_{19}H_{24}$
74910	90048	—	1,3-Propanediol, 2,2′-[(tetramethyl-*p*-phenylene)dimethylene]bis[2-methyl-, tetramethanesulfonate	$O_{12}S_4C_{24}H_{42}$
75141	90049	2917-96-6	2-Butyne-1,4-diol, dimethanesulfonate	$O_6S_2C_6H_{10}$
75339E	90035	—	5β-Cholane-3α,12α,24-triol, 3,12-dimethanesulfonate	$O_7S_2C_{29}H_{50}$
75751	90113	—	α-D-Altropyranoside, methyl 4,6-*O*-benzylidene-3-(cyanoamino)-3-deoxy-, methanesulfonate	$N_2O_7SC_{16}H_{20}$
75752	90114	—	α-D-Altropyranoside, methyl 3-(benzylcyanoamino)-4,6-*O*-benzylidene-3-deoxy-, methanesulfonate	$N_2O_7SC_{22}H_{24}$
75819	90050	—	2,3-Butanedione, 1,4-dihydroxy-, dimethanesulfonate	$O_8S_2C_6H_{10}$
75820	90082	—	1,2,4-Butanetriol, 1,4-dimethanesulfonate	$O_7S_2C_6H_{14}$
76303	90083	—	DL-Glycerol, 1,3-dimethanesulfonate	$O_7S_2C_5H_{12}$
76348	90115	—	α-D-Arabinofuranoside, methyl 3-amino-3-deoxy-5-thio-, 2-methanesulfonate, hydrochloride	$NO_5S_3C_7H_{15} \cdot HCl$
76349	90116	—	α-D-Glucofuranose, 1,2-*O*-isopropylidene-, 3,5,6-trimethanesulfonate	$O_{12}S_3C_{12}H_{22}$
76458	90051	—	Cyclohexane-*trans*-1,2-dimethanol, dimethanesulfonate	$O_6S_2C_{10}H_{20}$
76466	90225	—	9*H*-purine-6-thiol, 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-, 5′-methanesulfonate	$N_4O_6S_2C_{14}H_{18}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
77394	90242	—	1*H*-1,2,3-triazole-4,5-dimethanol, 1-phenyl-, dimethanesulfonate (methanesulfonic acid, [(1-phenyl-1*H*-1,2,3-triazole-4,5-diyl)-dimethylene]ester)	$N_3O_6S_2C_{12}H_{15}$
78789	90117	20720-17-6	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-, dimethanesulfonate	$O_{10}S_2C_{14}H_{26}$
79247	90118	—	D-Glucofuranose, 5-deoxy-1,2-*O*-isopropylidene-, 3-methanesulfonate, 6-*p*-nitrobenzoate	$NO_{10}SC_{17}H_{21}$
79422	90243	—	3-Quinuclidinol, methanesulfonate, hydrochloride	$NO_3SC_8H_{15} \cdot HCl$
79423	90168	6994-00-9	Ethanol, 2,2'-[(*p*-nitrosophenyl)imino]di-, dimethanesulfonate	$N_2O_7S_2C_{12}H_{18}$
79488	90119	—	α-D-*xylo*-Hexos-5-ene, 5,6-dideoxy-1,2-*O*-isopropylidene-, methanesulfonate (furo-[2,3-*d*]-1,3-dioxol-6-ol, 2,2-dimethyl-5-vinyl-, methanesulfonate)	$O_6SC_{10}H_{16}$
80100	90226	—	Adenine, 2-chloro-9-β-D-xylofuranosyl-, 2'-methanesulfonate	$N_5O_6SClC_{11}H_{14}$
80277	90208	—	Benzamide, *N*-[3-hydroxy-1-(hydroxymethyl)propyl]-, dimethanesulfonate	$NO_7S_2C_{13}H_{19}$
80565	89991	777-72-0	2-Indanol, methanesulfonate	$O_3SC_{10}H_{12}$
80585	90150	—	1,4-Butanediol, 2-amino-, 1-benzoate 4-methanesulfonate, methanesulfonate (salt)	$NO_6SC_{12}H_{17} : O_3SCH_4$
80604	90120	20706-72-3	D-Mannitol, 3,4-dimethanesulfonate	$O_{10}S_2C_8H_{18}$
80605	90121	20706-74-5	D-Mannitol, 1,2,5,6-tetraacetate 3,4-dimethanesulfonate	$O_{14}S_2C_{16}H_{26}$
80730	90122	—	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-4-*O*-(tetrahydropyran-2-yl)-, methanesulfonate	$O_9SC_{19}H_{32}$
80897	90151	—[a]	*threo*-1,2,3-Butanetriol, 4-(butylamino)-, 1-methanesulfonate, hydrochloride	$NO_5C_9H_{21} \cdot HCl$
80989	90209	—	Benzamide, *N*,*N*'-[DL-1,2-bis(hydroxymethyl)-ethylene]bis-, dimethanesulfonate	$N_2O_8S_2C_{20}H_{24}$
81678	90052	2590-37-6	*endo*-5-Norbornene-*cis*-2,3-dimethanol, dimethanesulfonate	$O_6S_2C_{11}H_{18}$
81679	90053	2434-86-8	*exo*-5-Norbornene-*cis*-2,3-dimethanol, dimethanesulfonate	$O_6S_2C_{11}H_{18}$
81680	90054	—	2-Norbornanemethanol, 6-hydroxy-3-phenyl-, dimethanesulfonate	$O_6S_2C_{16}H_{22}$
81684	90055	—	2-Norbornanecarboxylic acid, 5,6-dihydroxy-3-phenyl-, dimethanesulfonate	$O_8S_2C_{16}H_{20}$
81989	90123	20706-79-0	D-Mannitol, hexamethanesulfonate	$O_{12}S_6C_{12}H_{26}$
82218	90227	—	Adenine, 9-(3,5-anhydro-β-D-xylofuranosyl)-, 2'-methanesulfonate	$N_5O_5SC_{11}H_{13}$
82276	90169	—	Ethanol, 2,2'-(*m*-tolylimino)di-, dimethanesulfonate (ester)	$NO_6S_2C_{13}H_{21}$
82361	90170	—	Benzenediazonium, *p*-[bis(2-hydroxyethyl)-amino]-, tetrafluoroborate, dimethanesulfonate (ester)	$N_3O_6S_2C_{12}H_{18+} \cdot BF_4^- \; N_3O_6S_2BF_4C_{12}H_{18}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
82399	90084	—	L-1,2,4-Butanetriol, 1,4-dimethanesulfonate	$O_7S_2C_6H_{14}$
82856	90210	18303-74-7	DL-2,3-Butanediol, 1,4-bis(dimethylamino)-, dimethanesulfonate, dihydrochloride	$N_2O_6S_2C_{10}H_{24} \cdot 2HCl$
83062	90124	—	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-, 4-benzoate 3-methanesulfonate	$O_9SC_{20}H_{28}$
83215	90228	—	Uracil, 1-β-D-arabinofuranosyl-, 5′-benzoate 3′-methanesulfonate	$N_2O_9SC_{17}H_{18}$
83404	90125	24808-19-3	L-Iditol, 1,4:3,6-dianhydro-, dimethanesulfonate	$O_8S_2C_8H_{14}$
83405	90126	—	D-Glucitol, 1,4:3,6-dianhydro-5-deoxy-5-(dimethylamino)-, methanesulfonate, hydrochloride	$NO_5SC_9H_{17} \cdot HCl$
83636	90127	—	*myo*-Inositol, 1,4,5,6-tetramethanesulfonate	$O_{14}S_4C_{10}H_{22}$
83951	90211	—	DL-*threo*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)	$N_2O_6S_3C_6H_{16} \cdot 2(O_3SCH_4)$
84641	90158	—	1-Propanol, 3,3′-(methylimino)di-, dimethanesulfonate, hydrochloride	$NO_6S_2C_9H_{21} \cdot HCl$
85624	90212	—	L-*threo*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)	$N_2O_6S_3C_6H_{16} \cdot 2(O_3SCH_4)$
85625	90213	—	*erythro*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)	$N_2O_6S_3C_6H_{16} \cdot 2(O_3SCH_4)$
87907	90085	—	L-Threitol, 2,3-bis(hydrogen sulfate) 1,4-dimethanesulfonate, disodium salt	$O_{14}S_4C_6H_{14} \cdot 2\ Na$ salt
88191	90086	—	DL-*threo*-2,3-Butanediol, 1,4-bis(benzyloxy)-, dimethanesulfonate	$O_6S_2C_{20}H_{26}$
88792	90229	—	6*H*-furo[2′,3′:4,5]oxazolo[3,2-*a*]pyrimidin-6-one, 2,3,3a,9a-tetrahydro-3-hydroxy-2-(hydroxymethyl)-, 2-benzoate 3-methanesulfonate	$N_2O_9SC_{17}H_{16}$
90841	90230	—	Adenine, 2-chloro-9-(3,5-*O*-isopropylidene-β-D-xylofuranosyl)-, 2′-methanesulfonate	$N_4O_6SClC_{14}H_{19}$
91300	90214	27511-50-8	Methanesulfonamide, *N*,*N*′-[*meso*-1,2-bis(hydroxymethyl)ethylene]bis-, dimethanesulfonate	$N_2O_{10}S_4C_8H_{20}$
92133	90215	27511-26-8	Methanesulfonamide, *N*,*N*′-(*meso*-2,3-dihydroxytetramethylene)bis-, dimethanesulfonate; methanesulfonic acid, *meso*-1,2-bis(methanesulfonamidomethyl)ethylene ester	$N_2O_{10}S_4C_8H_{20}$
92318	90128	—	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-, methanesulfonate	$O_7SC_{22}H_{28}$
92319	90129	—	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-, dimethanesulfonate	$O_{10}S_2C_{22}H_{30}$
92320	90130	—	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-, methanesulfonate	$O_7SIC_{22}H_{27}$
92712	90131	13143-93-6	β-L-Arabinopyranoside, methyl, 2,3-dibenzoate 4-methanesulfonate	$O_9SC_{21}H_{22}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
92714	90132	13143-94-7	β-L-Arabinopyranoside, methyl, 4-methanesulfonate	$O_7SC_7H_{14}$
92952	90216	27511-27-9	Methanesulfonamide, *N,N'*-(DL-2,3-dihydroxytetramethylene)bis-, dimethanesulfonate	$N_2O_{10}S_4C_8H_{20}$
92953	90217	—	Methanesulfonamide, *N,N'*-(D-2,3-dihydroxytetramethylene)bis-, dimethanesulfonate	$N_2O_{10}S_4C_8H_{20}$
93100	90218	27511-51-9	Methanesulfonamide, *N,N'*-[DL-1,2-bis(hydroxymethyl)ethylene]bis-, dimethanesulfonate	$N_2O_{10}S_4C_8H_{20}$
93101	90219	27511-34-8	*p*-Toluenesulfonamide, *N,N'*-(*meso*-2,3-dihydroxytetramethylene)bis-, dimethanesulfonate	$N_2O_{10}S_4C_{20}H_{28}$
93651	90220	—	Carbamic acid, [D-1,2-bis(hydroxymethyl)-ethylene]di-, diethyl ester, dimethanesulfonate	$N_2O_{10}S_2C_{12}H_{24}$
94021	90221	—	1,2,5-Thiadiazolidine-DL-*trans*-3,4- dimethanol, 2,5-bis(methylsulfonyl)-, dimethanesulfonate, 1-oxide	$N_2O_{11}S_5C_6H_{14}$
94160	90087	2297-56-5	Erythritol, 1,4-dimethanesulfonate	$O_8S_2C_6H_{14}$
94318	90010	—	Salicylic acid, methanesulfonate	$O_5SC_7H_6$
94591	90056	—	*exo*-2,3-Norbornanedimethanol, 7-isopropylidene-, dimethanesulfonate	$O_6S_2C_{14}H_{24}$
94675	90231	—	Uridine, 2',5'-di-*O*-trityl-, 3'-methanesulfonate	$N_2O_9SC_{48}H_{42}$
94748	90222	—	Carbamic acid, (L-2,3-dihydroxytetramethylene)di-, diethyl ester, dimethanesulfonate	$N_2O_{10}S_2C_{12}H_{24}$
94749	90223	14737-63-4	Carbamic acid, [DL-1,2-bis(hydroxymethyl)-ethylene]di-, diethyl ester, dimethanesulfonate	$N_2O_{10}S_2C_{12}H_{24}$
97114	90232	7687-45-8	Adenine, 9-(2,3-*O*-isopropylidene-β-D-lyxofuranosyl)-, 5'-methanesulfonate	$N_5O_6SC_{14}H_{19}$
97115	90233	13516-39-7	Adenine, 9-(3-*S*-benzyl-3-thio-5-*O*-trityl-β-D-arabinofuranosyl)-, 2'-methanesulfonate	$N_5O_5S_2C_{37}H_{35}$
97728	90057	—	1,3-Propanediol, (*p*-methyl-α-phenylbenzyl)-, dimethanesulfonate	$O_6S_2C_{19}H_{24}$
97766	89992	—	4-Phenanthreneethanol, methanesulfonate	$O_3SC_{17}H_{16}$
97877	90205	—	Glycolamide, *N,N'*-(2-hydroxytrimethylene)-bis-, dimethanesulfonate (ester)	$N_2O_8S_2C_5H_{12}$
97891	90026	7031-65-4	1,4-Benzodioxan-2-methanol, methanesulfonate	$O_5SC_{10}H_{12}$
97892	90244	970-08-1	Phenothiazine-10-ethanol, α-methyl-, methanesulfonate	$NO_3S_2C_{16}H_{17}$
98767	90088	299-74-1	DL-Threitol, 1,4-dimethanesulfonate	$O_8S_2C_6H_{14}$
98931	90245	—	*as*-Triazin-3-ol, 5-phenyl-, methanesulfonate (ester)	$N_3O_3SC_{10}H_9$
100054	90133	7115-41-5	α-D-Xylofuranoside, ethyl 2-acetamido-2-deoxy-1-thio-, 3,5-dimethanesulfonate	$NO_6S_2C_{11}H_{21}$
100773	90152	—	Ethanol, 2-(*p*-nitroanilino)-, methanesulfonate (ester)	$N_2O_5SC_9H_{12}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
100774	90171	22974-35-2	Ethanol, 2,2′-[(*m*-nitrophenyl)imino]di-, dimethanesulfonate (ester)	$N_2O_8S_2C_{12}H_{18}$
101158	90234	—	Adenine, 9-(3-*S*-benzyl-3-thio-β-D-arabino-furanosyl)-, 2′-methanesulfonate	$N_5O_6S_3C_{18}H_{23}$
101671	90172	22964-43-8	Ethanol, 2,2′-[(*m*-chlorophenyl)imino]di-, dimethanesulfonate (ester)	$NO_6S_2ClC_{12}H_{18}$
101672	90173	22964-39-2	Ethanol, 2,2′-[(4-nitroso-*m*-tolyl)imino]di-, dimethanesulfonate (ester)	$N_2O_7S_2C_{13}H_{20}$
101673	90174	23721-18-8	Ethane, 2,2′-[(*p*-nitrophenyl)imino]di-, dimethanesulfonate (ester)	$N_2O_8S_2C_{12}H_{18}$
101674	90175	22964-47-2	Benzoic acid, *m*-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate (ester)	$NO_8S_2C_{13}H_{21}$
101761	90153	18677-88-8	Uracil, 5-[bis(2-hydroxyethyl)amino]1,3-dityrityl-, 5-methanesulfonate (ester)	$N_2O_6SC_{47}H_{42}$
102467	90176	22964-40-5	Ethanol, 2,2′-[(3-chloro-4-nitrosophenyl)-imino]di-, dimethanesulfonate	$N_2O_7S_2ClC_{12}H_{17}$
102468	90177	22964-46-1	Ethanol, 2,2′-[α,α,α-trifluoro-*m*-tolyl)imino]-di-, dimethanesulfonate	$NO_6S_2F_3C_{13}H_{18}$
102469	90178	3721-13-3	Ethanol, 2,2′-[(*m*-aminophenyl)imino]di-, dimethanesulfonate, monohydrochloride	$N_2O_6S_2C_{12}H_{20} \cdot HCl$
102627	90159	3458-22-8	1-Propanol, 3,3′-iminodi-, dimethanesulfonate (ester), hydrochloride	$NO_6S_2C_9H_{21} \cdot HCl$
102820	90058	—	*trans*-1,3-Cyclobutanediol, 2,2,4,4-tetramethyl-, dimethanesulfonate	$O_6S_2C_{10}H_{20}$
103362	90179	23721-22-4	Benzoic acid, 5-[bis(2-hydroxyethyl)amino]-2-nitro-, ethyl ester, dimethanesulfonate	$N_2O_{10}S_2C_{13}H_{22}$
103363	90180	22964-44-9	Ethanol, 2,2′-[(*m*-fluorophenyl)imino]di-, dimethanesulfonate	$NO_6S_2FC_{12}H_{18}$
103961	90181	22964-41-6	Ethanol, 2,2′-[(3-fluoro-4-nitrosophenyl)-imino]di-, dimethanesulfonate (ester)	$N_2O_7S_2FC_{12}H_{17}$
103962	90182	23721-23-5	Benzoic acid, 2-amino-5-[bis(2-hydroxyethyl)-amino]-, ethyl ester, dimethanesulfonate (ester), monohydrochloride	$N_2O_8S_2C_{13}H_{24} \cdot HCl$
104962	90183	23721-20-2	Ethanol, 2,2′-[(3-fluoro-4-nitrophenyl)imino]-di-, dimethanesulfonate (ester)	$N_2O_8S_2FC_{12}H_{17}$
104963	90184	23721-21-3	Ethanol, 2,2′-[(α,α,α-trifluoro-4-nitro-*m*-tolyl)-imino]di-, dimethanesulfonate (ester)	$N_2O_8S_2F_3C_{13}H_{17}$
104964	90185	22964-42-7	Acetanilide, 3′-[bis(2-hydroxyethyl)amino]-6′-nitroso-, dimethanesulfonate (ester)	$N_3O_8S_2C_{14}H_{21}$
104965	90186	23721-19-9	Ethanol, 2,2′-[(3-chloro-4-nitrophenyl)imino]-di-, dimethanesulfonate (ester)	$N_2O_8S_2ClC_{12}H_{17}$
104967	90187	22964-45-0	Acetanilide, 3′-[bis(2-hydroxyethyl)amino]-, dimethanesulfonate (ester)	$N_2O_7S_2C_{14}H_{22}$
105411	90134	—	α-D-*erythro*-Hexopyranoside, ethyl 2,3,6-trideoxy-6-iodo-, methanesulfonate	$O_5SIC_9H_{17}$
106308	90059	29166-53-8	Methanesulfonic acid, chloro-, tetramethylene ester	$O_3S_2Cl_2C_4H_{12}$
106625	90206	3415-55-2	Ethanol, 2,2′-[tetramethylenebis(methyl-	$N_2O_6S_2C_{12}H_{28} \cdot HCl$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
			imino)]di-, dimethanesulfonate (ester), monohydrochloride	
106754	90235	15023-78-6	Adenine, 9-(3,5-*O*-isopropylidene-4-thio-β-D-xylofuranosyl)-, 2′-methanesulfonate	$N_5O_6S_2C_{14}H_{19}$
106760	90135	—	α-D-Xylofuranoside, methyl, 2-methanesulfonate	$O_7SC_7H_{14}$
106788	89993	—	2-Propen-1-ol, 2,3-dibromo-, methanesulfonate	$O_3SBr_2C_4H_6$
106905	89994	—	Cyclohexanemethanol, 1-phenyl-, methanesulfonate	$O_3SC_{14}H_{20}$
106906	90027	—	1,4-Benzodioxan-2-methanol, 5-methoxy-, methanesulfonate, mixt. with (8-methoxy-1,4-benzodioxan-2-yl) methyl methanesulfonate	$O_6SC_{11}H_{14}$
107184	90236	—	Adenine, 9-[3-deoxy-3-[(dithiocarboxy)-amino]-5-*O*-trityl-β-D-arabinofuranosyl]-*N*-trityl-, methyl ester, 2′-methanesulfonate	$N_6O_5S_3C_{51}H_{45}$
107400	90237	15023-76-4	Adenine, 9-(4-thio-β-D-xylofuranosyl)-, 2′-methanesulfonate	$N_5O_5S_2C_{11}H_{15}$
107401	90136	—	α-L-*arabino*-Hexopyranoside, methyl 2,6-dideoxy-, dimethanesulfonate	$O_6S_2C_9H_{18}$
107635	90060	—	*cis*-1,3-Cyclobutanediol, 2,2,4,4-tetramethyl-, dimethanesulfonate	$O_6S_2C_{10}H_{20}$
108033	89995	—	1-Propanesulfonic acid, 3-hydroxy-, methanesulfonate	$O_6S_2C_4H_{10}$
108083	90137	—	L-*ribo*-Hexopyranoside, methyl 3-azido-2,3,6-trideoxy-, 4-methanesulfonate, α-	$N_3O_6SC_8H_{15}$
108084	90138	—	Arabinopyranoside, methyl 3,4-*O*-isopropylidene-, methanesulfonate, β-D-	$O_7SC_{10}H_{18}$
109265	90154	—	2-Propanol, 1,1′-[[(2-hydroxy-1-naphthyl)-methyl]imino]di-, 2-methanesulfonate	$NO_6SC_{18}H_{25}$
109522	90139	18981-62-9	L-*arabino*-Hexopyranoside, methyl 3-azido-2,3,6-trideoxy-, 4-methanesulfonate, α-	$N_3O_6SC_8H_{15}$
110474	90011	—	1-Naphthol, 2,4-dichloro-, methanesulfonate	$O_3SCl_2C_{11}H_8$
110557	90012	—	Hydroquinone, 2,5-dichloro-, methanesulfonate	$O_5SCl_2C_7H_6$
110558	90013	—	Hydroquinone, 2,5-dichloro-, dimethanesulfonate	$O_6S_2Cl_2C_8H_8$
110559	90246	25795-97-5	2-Pyridinol, methanesulfonate (ester)	$NO_3SC_6H_7$
110560	90014	—	Phenol, 2,2′-methylenebis[3,4,6-trichloro-, dimethanesulfonate	$O_6S_2Cl_4C_{15}H_{10}$
110561	90247	25171-77-1	2-Pyridinol, 3,5-dichloro-, methanesulfonate (ester)	$NO_3SCl_2C_6H_5$
110562	90248	—	8-Quinolinol, 5-bromo-, methanesulfonate (ester)	$NO_3SBrC_{10}H_8$
110563	90249	25171-74-8	2-Pyridinol, 5-chloro-, methanesulfonate (ester)	$NO_3SClC_6H_6$
110564	90015	—	Hydroquinone, tetrachloro-, dimethanesulfonate	$O_6S_2Cl_4C_8H_6$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
110565	90016	—	Phenol, 2,2′-thiobis[4,6-dichloro-, dimethanesulfonate	$O_6S_3Cl_4C_{14}H_{10}$
110676	90250	—	2-Benzimidazolepropanol, 1-(methylsulfonyl)-, methanesulfonate (ester)	$N_2O_5S_2C_{12}H_{16}$
110899	90017	—	Coumarin, 7-hydroxy-4-methyl-, methanesulfonate	$O_5SC_{11}H_{10}$
110900	90018	—	*m*-Cresol, *α,α,α*-trifluoro-, methanesulfonate	$O_3SF_3C_8H_7$
110901	90019	—	5-Indanol, methanesulfonate	$O_3SC_{10}H_{12}$
110902	90020	—	1-Naphthol, 4-chloro-, methanesulfonate	$O_3SClC_{11}H_9$
110903	90021	—	2-Naphthol, 1-nitro-, methanesulfonate	$NO_5SC_{11}H_9$
110905	90251	27160-67-4	8-Quinolinol, 5,7-dibromo-, methanesulfonate (ester)	$NO_3SBr_2C_{10}H_7$
110906	90252	27092-50-8	8-Quinolinol, 5,7-dichloro-, methanesulfonate (ester)	$NO_3SCl_2C_{10}H_7$
110907	90022	—	2-Naphthol, 6-bromo-, methanesulfonate	$O_3SBrC_{11}H_9$
111709	90140	—	Xylopyranoside, methyl 3-acetamido-3-deoxy-, dimethanesulfonate (ester), L-	$NO_8S_2C_{10}H_{19}$
112864	90141	—	Arabinopyranoside, methyl, 2-methanesulfonate, *β*-D-	$O_7SC_7H_{14}$
112898	90253	—	2-Benzimidazolemethanol, 1-acetyl-, methanesulfonate (ester)	$N_2O_4SC_{11}H_{12}$
113472	90142	—	Arabinopyranoside, methyl 3,4-di-*O*-methyl-, methanesulfonate, *β*-D-	$O_7SC_9H_{18}$
114012	90143	—	Galactitol, 2,4:3,5-di-*O*-isopropylidene-, dimethanesulfonate, D-	$O_{10}S_2C_{14}H_{26}$
115485	90160	27687-73-6	Ethanol, 2,2′-(methylimino)di-, dimethanesulfonate (ester), hydrochloride	$NO_6S_2C_7H_{17}$ · HCl
116866	89996	—	Cyclohexanol, 2-(*m*-methoxyphenyl)-, methanesulfonate, *trans*-	$O_4SC_{14}H_{20}$
116867	89997	—	Cyclohexanol, 2-(*p*-methoxyphenyl)-, methanesulfonate, *trans*-	$O_4SC_{14}H_{20}$
116868	89998	—	Cycloheptanol, 2-(2,3,4-trimethoxyphenyl)-, methanesulfonate, *trans*-	$O_6SC_{17}H_{26}$
116869	89999	—	Cyclohexanol, 2-(*o*-methoxyphenyl)-, methanesulfonate, *trans*-	$O_4SC_{14}H_{20}$
116870	90000	—	Cyclohexanol, 2-*o*-tolyl-, methanesulfonate, *trans*-	$O_3SC_{14}H_{20}$
116871	90001	—	Cyclohexanol, 2-*m*-tolyl-, methanesulfonate, *trans*-	$O_3SC_{14}H_{20}$
116872	90002	—	Cyclohexanol, 2-*p*-tolyl-, methanesulfonate, *trans*-	$O_3SC_{14}H_{20}$
116873	90003	—	Cyclohexanol, 2-phenyl-, methanesulfonate, *trans*-	$O_3SC_{13}H_{18}$
116874	90028	—	3-Benzothiepin-1-ol-, 1,2,4,5-tetrahydro-, methanesulfonate	$O_3S_2C_{11}H_{14}$
116875	90029	—	Thiochroman-4-ol, methanesulfonate, 1,1-dioxide	$O_5S_2C_{10}H_{12}$

TABLE A.—List of agents tested—Continued

NSC No.	Entry No.	CAS reg. No.	Compound name	Molecular formula
116876	90030	—	Isothiochroman-4-ol, methanesulfonate, 2,2-dioxide	$O_5S_2C_{10}H_{12}$
116877	90031	—	1-Benzothiepin-5-ol, 2,3,4,5-tetrahydro-, methanesulfonate	$O_3O_2C_{11}H_{14}$
117359	90144	—	Galactitol, 1,6-dimethanesulfonate, D-	$O_{10}S_2C_8H_{18}$
117379	90004	—	Acrylic acid, 2-cyano-3-hydroxy-, methanesulfonate (ester)	$NO_5SC_5H_5$
117537	90061	—	3-Cyclohexene-1,1-dimethanol, dimethanesulfonate	$O_6S_2C_{10}H_{18}$
120389	90062	—	1,2-Cyclohexanedimethanol, dimethanesulfonate	$O_6S_2C_{10}H_{20}$
122284	90063	—	Poly[1,2-bis[[(methylsulfonyl)oxy]methyl]-3-ethoxytetramethylene]	$(O_7S_2C_{10}H_{20})n$
122402	90207	—	Erythritol, 1,4-dideoxy-1,4-bis[(2-hydroxyethyl)amino]-, 1,4-dimethanesulfonate (ester), *meso*-	$N_2O_8S_2C_{10}H_{24}$
122610	90005	—	Cyclohexanol, 2-phenyl-, methanesulfonate	$O_3SC_{13}H_{18}$
122801	90145	—	Mannitol, 2,3:4,5-di-*O*-methylene-, dimethanesulfonate, D-	$O_{10}S_2C_{10}H_{18}$
400288	90146	7512-01-8	D-Glucose, 1,2-*O*-isopropylidene-, 5,6-diacetate, 3-methanesulfonate	$O_{10}SC_{14}H_{22}$
400293	90147	7702-26-3	α-D-Ribose, 1,3,5-tribenzoate, 2-methanesulfonate	$O_{10}SC_{27}H_{24}$
407721	90064	7495-52-5	1,3-Propanediol, 2-(*o*-bromo-α-phenylbenzyl)-, dimethanesulfonate	$O_6S_2BrC_{18}H_{21}$
407733	90065	—	1,3-Propanediol, 3-(di-1-naphthylmethyl)-, dimethanesulfonate	$O_6S_2C_{29}H_{28}$
409597	90066	—	1,3,5-Cyclohexanetrimethanol, trimethanesulfonate	$O_9S_3C_{12}H_{24}$

TABLE 1.—Assay systems*

Test systems	Host strain	Tumor inoculum† Type	Tumor inoculum† Route	Treatment route	Treatment schedule	Parameter of response‡
L1210, early	CDBA, BDF_1	AF	ip	ip	qd, Days 1–10 qd, Day 1–death	ILS
L1210, advanced	CDBA, BDF_1	—	sc	sc	qd, Day 5–death	ILS
W-256 (im)	Albino rat	TS	im	ip	qd, Days 3–6	TWI, Day 7
CA-755	BDF_1	TF	sc	ip	qd, Days 1–11	TWI, Day 12
S-180	Swiss	TF	sc	ip	qd, Days 1–17	TWI, Day 8
LL	BDF_1	TF	sc	ip	qd, Days 1–11	TWI, Day 12
KB§						ED50

*In in vivo testing, treatment started 24 hours after tumor implantation. All response values are expressed as percentages relative to an untreated tumor-bearing control group.

†Im = intramuscular inoculation of tumor; ip = intraperitoneal; sc = subcutaneous; AF = ascites fluid; TS = tumor suspension; TF = tumor fragment; qd = daily.

‡For L1210, drugs demonstrating a 25% increase in lifespan over controls (ILS) may be considered as active on the grounds that it is ordinarily a significant and reproducible effect. The other tumor systems employ tumor weight inhibition (TWI) as the criterion of effect. A 75% inhibition in tumor weight relative to controls, at the optimal dose (OD: LD10 approximately) is usually indicative of activity.

§KB = human epidermoid carcinoma of the nasopharynx. ED50 is the calculated effective dose in μg/ml which inhibits growth, based on protein determination, to 50% of controls.

TABLE 2.—Summary of spectrum of activity in Division of Cancer Treatment (formerly Chemotherapy) screens

TABLE 2.—Summary of spectrum of activity in Division of Cancer Treatment (formerly Chemotherapy) screens

Group No.	Total No. of compounds examined	L1210		W-256		CA-755		S-180		LL		KB	
		A/T* (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)
1	29	1/25	52142	3/10	50256 67176 106788	1/8	18016	0/10	—	-/0	—	0/7	—
2	17	0/16	—	0/9	—	0/4	—	0/4	—	-/0	—	0/1	—
3	9	0/6	—	-/0	—	.0/1	—	0/1	—	-/0	—	0/4	—
4	4	0/3	—	-/0	—	-/0	—	0/4	—	-/0	—	0/1	—
5	31	1/15	3052	4/8	750 3052 17019 106308	1/6	17017	0/10	—	0/2	—	0/19	—
6	22	1/3	39069	1/2	39069	2/5	39069 82399	0/2	—	0/2	—	0/20	—
7	59	0/36	—	1/8	37538	0/19	—	0/22	—	0/6	—	0/36	—
8	7	0/4	—	0/1	—	0/1	—	0/1	—	-/0	—	0/4	—
9	6	3/3	84641 102627 115485	0/1	—	-/0	—	-/0	—	-/0	—	0/4	—
10	27	15/26	54012 72151 79423 82361 100774 101671 101672 102467 102468 102469 103363 103961 103962 104965 104967	16/18	24820 54012 59640 59643 71035 72151 79423 82361 100774 101674 102468 103961 103962 104964 104965 104967	-/0	—	-/0	—	-/0	—	4/13	79423 103363 103961 104964
11	5	2/5	47774 61147	2/2	47774 61147	2/5	47774 61147	0/5	—	0/1	—	-/0	—

*A = active, T = tested.

TABLE 2.—Summary of spectrum of activity in Division of Cancer Treatment (formerly Chemotherapy) screens—Continued

Group No.	Total No. of compounds examined	L1210		W-256		CA-755		S-180		LL		KB	
		A/T* (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)	A/T (No.)	A (NSC No.)
12	15	6/12	24901 57844 58825 61151 106625 122402	5/6	24901 55109 57844 61151 106625	7/11	24901 53582 55109 55110 55111 57844 61154	0/8	—	0/1	—	1/8	53582
13	16	–/0	—	–/0	—	–/0	—	–/0	—	–/0	—	0/16	—
14	14	0/6	—	–/0	—	0/1	—	0/3	—	0/3	—	0/11	—
15	16	0/13	—	0/5	—	0/3	—	0/4	—	–/0	—	0/5	—

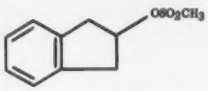
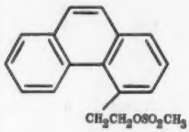
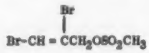
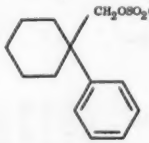
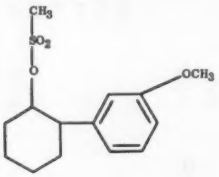
*A = active, T = tested.

TABLE 3.—Group 1: alkyl and cyclic alkyl methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
89977	3718	Methanesulfonic acid CH_3SO_2OH			50–(400*)	0							
89978	17018	Methanesulfonic acid, 2-phenoxyethyl ester $CH_3SO_2OCH_2CH_2O$–	170†	3			135†	0	170†	6			
89979	18016	Ethanol, 2-chloro-, methanesulfonate $CH_3SO_2OCH_2CH_2Cl$	75	2	100	70	140	79	53	7			>100
89980	20669	Methanesulfonic acid, pentyl ester $CH_3SO_2OCH_2(CH_2)_3CH_3$	125†	5	100†	0			125	18			
89981	24897	Glycolic acid, methanesulfonate $CH_3SO_2OCH_2COOH$							(75,300*)	0			
89982	26358	Methanesulfonic acid, 2-cyanoethyl ester $CH_3SO_2OCH_2CH_2CN$	450†	0					500†	5			
89983	26805	Methanesulfonic acid, ethyl ester $CH_3SO_2OCH_2CH_3$	140†	8	140†	62			(125,500*)	0			>100
89984	36060	Methanesulfonic acid, butyl ester $CH_3SO_2OCH_2CH_2CH_2CH_3$	200†	0			200†	15	250†	2			
89985	49507	Methanesulfonic acid, 3-chloropropyl ester $CH_3SO_2O(CH_2)_2CH_2Cl$	110†	0			55	13	125	6			
89986	49551	Ethanol, 2-bromo-, methanesulfonate $CH_3SO_2OCH_2CH_2Br$	60	7	25	24	60†	2	65	15			100
89987	49872	Methanesulfonic acid, propyl ester $CH_3SO_2O(CH_2)_2CH_3$	400	18	400	58	(175–350*)	0	500†	46			
89988	50256	Methanesulfonic acid, methyl ester $CH_3SO_2OCH_3$	50	10	100	95	50	12					28
89989	52142	Methanesulfonic acid, 2-fluoroethyl ester $CH_3SO_2OCH_2CH_2F$	100‡	45			8.0	43					>100

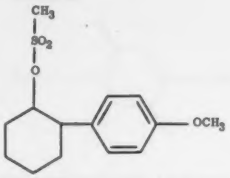
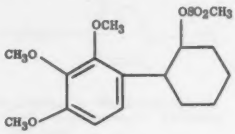
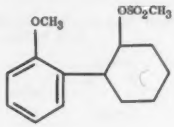
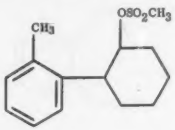
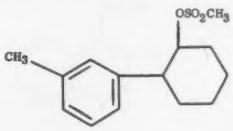
*Toxic dose.
†Only dose tested.
‡Single treatment. OD > LD10.

TABLE 3.—Group 1: alkyl and cyclic alkyl methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
89990	67176	Methanesulfonic acid, 4-hydroxybutyl ester	400†	20	200	92							
		$CH_3SO_2OCH_2(CH_2)_2CH_2OH$											
89991	80565	2-Indanol, methanesulfonate											>100
													
89992	97766	4-Phenanthreneethanol, methanesulfonate											100
													
89993	106788	2-Propen-1-ol, 2,3-dibromo-, methanesulfonate	150†	8	150†	87							
													
89994	106905	Cyclohexanemethanol, 1-phenyl-, methanesulfonate	400§	8									
													
89995	108033	1-Propanesulfonic acid, 3-hydroxy-, methanesulfonate	100†	8	100†	42							
		$CH_3SO_2OCH_2CH_2CH_2SO_2OH$											
89996	116866	Cyclohexanol, 2-(*m*-methoxyphenyl)-, methanesulfonate, *trans*-	(100–400)§	0									
													

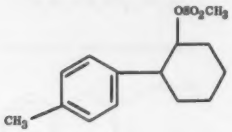
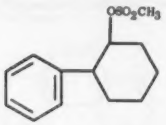
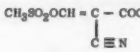
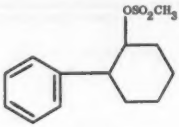
†Only dose tested.
§Single treatment.

TABLE 3.—Group 1: alkyl and cyclic alkyl methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		J.J.		[illegible]
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	E [illegible]
89997	116867	Cyclohexanol, 2-(*p*-methoxyphenyl)-, methanesulfonate, *trans*-	200§	6									
													
89998	116868	Cycloheptanol, 2-(2,3,4-trimethoxyphenyl)-, methanesulfonate, *trans*-	200§	19									
													
89999	116869	Cyclohexanol, 2-(*o*-methoxyphenyl), methanesulfonate, *trans*-	200§	11									
													
90000	116870	Cyclohexanol, 2-*o*-tolyl-, methanesulfonate, *trans*-	(100–400)§	0									
													
90001	116871	Cyclohexanol, 2-*m*-tolyl-, methanesulfonate, *trans*-	200§	8									
													

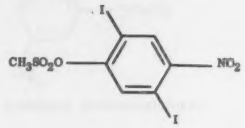
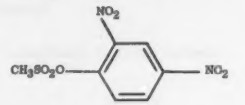
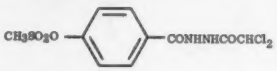
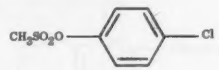
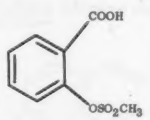
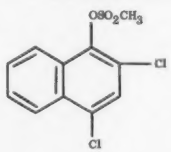
§Single treatment.

TABLE 3.—Group 1: alkyl and cyclic alkyl methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90002	116872	Cyclohexanol, 2-*p*-toyl-, methanesulfonate, *trans*-	(100–400)§	0									
													
90003	116873	Cyclohexanol, 2-phenyl-, methanesulfonate, *trans*-	100§	3									
													
90004	117379	Acrylic acid, 2-cyano-3-hydroxy-, methanesulfonate (ester)	200§	6									
													
90005	122610	Cyclohexanol, 2-phenyl-, methanesulfonate	40†	0									
													

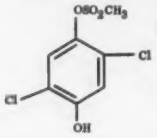
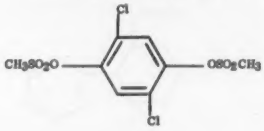
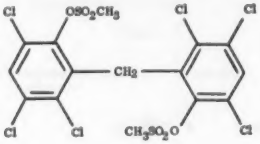
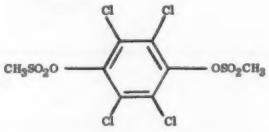
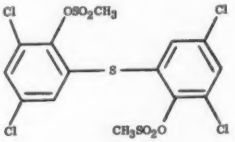
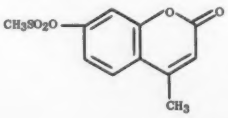
§Single treatment.
†Only dose tested.

TABLE 3.—Group 2: aromatic methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90006	19784	Methanesulfonic acid, 2,5-diiodo-4-nitrophenyl ester (phenol, 2,5-diiodo-4-nitro-, methanesulfonate)	125†	22			56	28	125	23			
													
90007	19785	Methanesulfonic acid, 2,4-dinitrophenyl ester (phenol, 2,4-dinitro-, methanesulfonate)	62†	20			56	32	62	26			
													
90008	29838	Hydrazine, 1-(dichloroacetyl)-2-(p-hydroxybenzoyl)-, methanesulfonate	350†	0			350†	51	375†	44			
													
90009	40485	Methanesulfonic acid, p-chlorophenyl ester	113†	0			113†	4	125	4			
													
90010	94318	Salicylic acid, methanesulfonate											>99
													
90011	110474	1-Naphthol, 2,4-dichloro-, methanesulfonate	400†	0	400†	0							
													

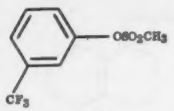
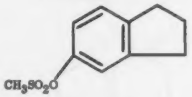
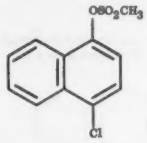
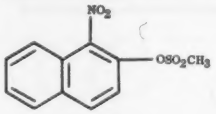
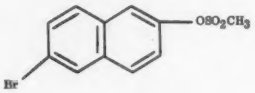
†Only dose tested.

TABLE 3.—Group 2: aromatic methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90012	110557	Hydroquinone, 2,5-dichloro-, methanesulfonate	200†	0	200†	0							
													
90013	110558	Hydroquinone, 2,5-dichloro-, dimethanesulfonate	400†	0	400†	34							
													
90014	110560	Phenol, 2,2′-methylenebis[3,4,6-trichloro-, dimethanesulfonate	400†	0	400†	21							
													
90015	110564	Hydroquinone, tetrachloro-, dimethanesulfonate	200	1	200†	0							
													
90016	110565	Phenol, 2,2′-thiobis[4,6-dichloro-, dimethanesulfonate	(200–400*)	0	200†	19							
													
90017	110899	Coumarin, 7-hydroxy-4-methyl-, methanesulfonate	100‡	13	400†	20							
													

*Toxic dose.
†Only dose tested.
‡Single treatment.

TABLE 3.—Group 2: aromatic methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90018	110900	*m*-Cresol, α,α,α-trifluoro-, methanesulfonate	100‖	7									
													
90019	110901	5-Indanol, methanesulfonate	400†	0									
													
90020	110902	1-Naphthol, 4-chloro-, methanesulfonate	400†	0	400†	15							
													
90021	110903	1-Naphthol, 1-nitro-, methanesulfonate	400†	0	400†	24							
													
90022	110907	2-Naphthol, 6-bromo-, methanesulfonate	400†	0									
													

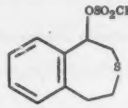
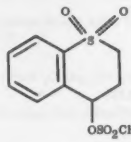
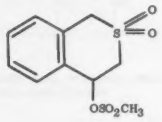
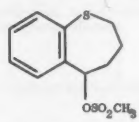
†Only dose tested.
‖Single treatment.

TABLE 3.—Group 3: heterocyclic methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90023	19788	4*H*-pyran-4-one, 5-hydroxy-2-(hydroxymethyl)-, dimethanesulfonate	125†	13			56	3	125	16			>100
90024	68223	4*H*-pyran-4-one, 5-hydroxy-2-(hydroxymethyl)-, 2-acetate, 5-methanesulfonate											22
90025	73494	1-Benzothiepin-5-ol, 2,3,4,5-tetrahydro-, 1,1-dioxide, methanesulfonate											>100
90026	97891	1,4-Benzodioxan-2-methanol, methanesulfonate											54
90027	106906	1,4-Benzodioxan-2-methanol, 5-methoxy-, methanesulfonate, mixt. with (8-methoxy-1,4-benzodioxan-2-yl)methyl methanesulfonate	(100–400)§	0									

†Only dose tested.
§Single treatment.

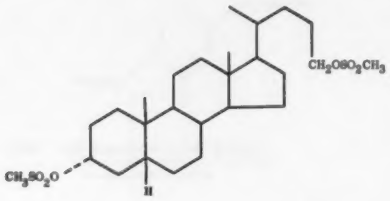
TABLE 3.—Group 3: heterocyclic methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90028	116874	3-Benzothiepin-1-ol-, 1,2,4,5-tetrahydro-, methanesulfonate	50§	4									
													
90029	116875	Thiochroman-4-ol, methanesulfonate, 1,1-dioxide	(100–400)§	0									
													
90030	116876	Isothiochroman-4-ol, methanesulfonate, 2,2-dioxide	(100–400)§	1									
													
90031	116877	1-Benzothiepin-5-ol, 2,3,4,5-tetrahydro-, methanesulfonate	100§	3									
													

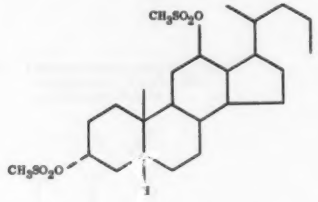
§Single treatment.

TABLE 3.—Group 4: steroid methanesulfonates

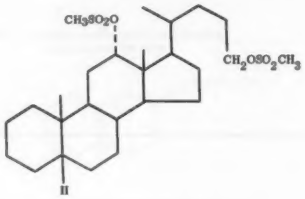
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90032	67657E	5β-Cholane-3α, 24-diol, dimethanesulfonate	2	14					0.25	8			



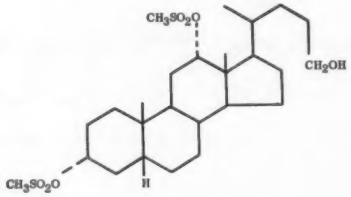
90033	67658E	5β-Cholane-3α, 12α-diol, dimethanesulfonate	100†	0					125†	0			



90034	67659E	5β-Cholane-12α, 24-diol, dimethanesulfonate	100†	0					125†	0			

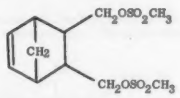
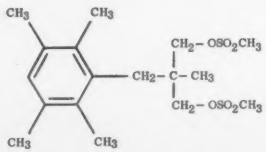


90035	75339E	5β-Cholane-3α, 12α, 24-triol, 3,12-dimethanesulfonate							500†	36			24



†Only dose tested.

TABLE 3.—Group 5: two or more methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90036	750	1,4-Butanediol, dimethanesulfonate	12.5	17	26	80	40	50	39	40			20
		$CH_3SO_2OCH_2(CH_2)_2CH_2OSO_2CH_3$											
90037	3052	1,9-Nonanediol, dimethanesulfonate	108	31	100	83	16	74	62.5	30	50	50	
		$CH_3SO_2O(CH_2)_9OSO_2CH_3$											
90038	17016	Methanesulfonic acid, ethylene ester	170†	0					170†	0			
		$CH_3SO_2OCH_2CH_2OSO_2CH_3$											
90039	17017	Methanesulfonic acid, trimethylene ester	170	7			30	75	57	47			100
		$CH_3SO_2O(CH_2)_3OSO_2CH_3$											
90040	17019	1,5-Pentanediol, dimethanesulfonate	25	15	25	95	12.5	50	50	60			24
		$CH_3SO_2O(CH_2)_5OSO_2CH_3$											
90041	23890	2,5-Hexanediol, dimethanesulfonate	16	10	15	66	7.5	8	12.5	23			
		$CH_3SO_2OCH(CH_3)(CH_2)_2CH(CH_3)OSO_2CH_3$											
90042	24899	Glycolic acid, ethylene ester, dimethanesulfonate	90†	4	90†	47			(100–500*)	0			
		$CH_3SO_2OCH_2C(=O)OCH_2CH_2OC(=O)CH_2OSO_2CH_3$											
90043	24900	Glycolic acid, 2-hydroxyethyl ester, dimethanesulfonate							500†	toxic			
		$CH_3SO_2OCH_2CH_2OC(=O)CH_2OSO_2CH_3$											
90044	54688	*trans*-5-Norbornene-2,3-dimethanol, dimethanesulfonate	175	20			350†	8	500†	29			
													
90045	58819	2-Propanone, 1,3-dihydroxy-, dimethanesulfonate	10	16									5.9
		$CH_3SO_2OCH_2C(=O)CH_2OSO_2CH_3$											
90046	74885	1,3-Propanediol, 2-methyl-2-(2,3,5,6-tetramethylbenzyl)-, dimethanesulfonate											>100
													

*Toxic dose.
†Only dose tested.

TABLE 3.—Group 5: two or more methanesulfonates without nitrogen—Continued

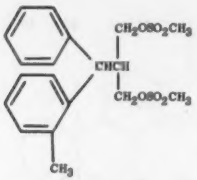
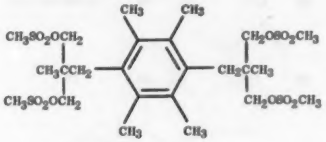
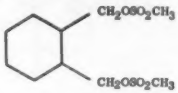
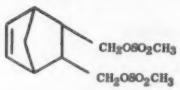
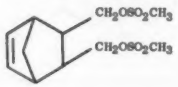
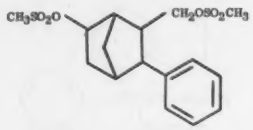
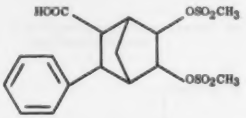
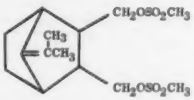
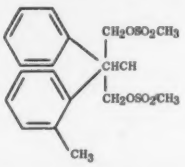
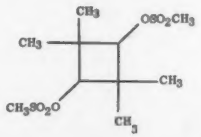
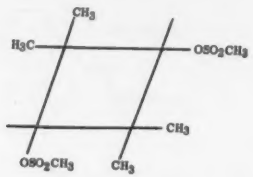
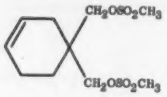
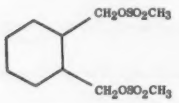
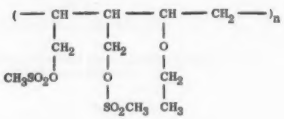
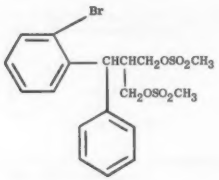
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED_{50}
90047	74902	1,3-Propanediol, 2-(*o*-methyl-*α*-phenylbenzyl)-, dimethanesulfonate											66
													
90048	74910	1,3-Propanediol, 2,2'-[(tetramethyl-*p*-phenylene)dimethylene]-bis[2-methyl-, tetramethanesulfonate											>100
													
90049	75141	2-Butyne-1,4-diol, dimethanesulfonate	64	17					20	16	16	9	1.3
90050	75819	2,3-Butanedione, 1,4-dihydroxy-, dimethanesulfonate											>100
90051	76458	Cyclohexane-*trans*-1,2-dimethanol, dimethanesulfonate											100
													
90052	81678	*endo*-5-Norbornene-*cis*-2,3-dimethanol, dimethanesulfonate											>100
													
90053	81679	*exo*-5-Norbornene-*cis*-2,3-dimethanol, dimethanesulfonate											>100
													

TABLE 3.—Group 5: two or more methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90054	81680	2-Norbornanemethanol, 6-hydroxy-3-phenyl-, di...ethanesulfonate											>100
													
90055	81684	2-Norbornanecarboxylic acid, 5,6-dihydroxy-3-phenyl-, dimethanesulfonate											28
													
90056	94591	*exo*-2,3-Norbornanedimethanol, 7-isopropylidene-, dimethanesulfonate											29
													
90057	97728	1,3-Propanediol, (*p*-methyl-*α*-phenylbenzyl)-, dimethanesulfonate											28
													
90058	102820	*trans*-1,3-Cyclobutanediol, 2,2,4,4-tetramethyl-, dimethanesulfonate	200	1	200†	8							
													
90059	106308	Methanesulfonic acid, chloro-, tetramethylene ester			150	91							
		$ClCH_2SO_2OCH_2(CH_2)_2CH_2OSO_2CH_2Cl$											

†Only dose tested.

TABLE 3.—Group 5: two or more methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90060	107635	*cis*-1,3-Cyclobutanediol, 2,2,4,4-tetramethyl-, dimethanesulfonate	400†	8	400†	0							
													
90061	117537	3-Cyclohexene-1,1-dimethanol, dimethanesulfonate	400†	0									
													
90062	120389	1,2-Cyclohexanedimethanol, dimethanesulfonate	400†§	0									10
													
90063	122284	Poly[1,2-bis [[(methylsulfonyl)-oxy]methyl]-3-ethoxytetramethylene]	400†	6									
													
90064	407721	1,3-Propanediol, 2-(o-bromo-α-phenylbenzyl)-, dimethanesulfonate											46
													

†Only dose tested.
§Single treatment.

TABLE 3.—Group 5: two or more methanesulfonates without nitrogen—Continued

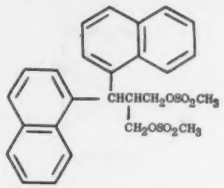
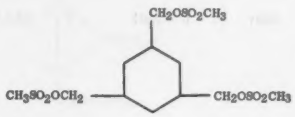
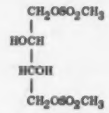
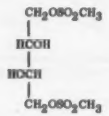
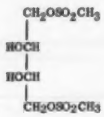
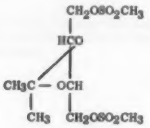
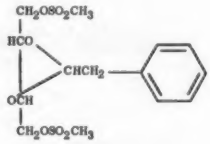
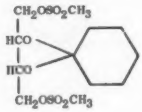
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90065	407733	1,2-Propanediol, 3-(di-1-naphthylmethyl)-, dimethanesulfonate											>100
													
90066	409597	1,3,5-Cyclohexanetrimethanol, trimethanesulfonate											10
													

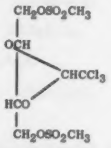
TABLE 3.—Group 6: three- and four-carbon sugar methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90067	39068	D-Threitol, 1,4-bis(methanesulfonate)									1000	45	3.0
													
90068	39069	L-Threitol, 1,4-dimethanesulfonate	1000	32	1600	96	500	94					
													
90069	39070	Erythritol, 1,4-bis(methanesulfonate)	200†	0			200†	0	250†	7	62.5	29	5.4
													
90070	60499	L-Threitol, 2,3-*O*-isopropylidene-, dimethanesulfonate	450†	4			450†	0	500†	0			>100
													
90071	63325	L-Threitol, 2,3-*O*-phenethylidene-, dimethanesulfonate											>100
													
90072	63379	Erythritol, 2,3-*O*-cyclohexylidene-, dimethanesulfonate											>100
													

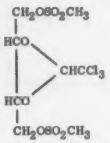
†Only dose tested.

TABLE 3.—Group 6: three- and four-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90073	65402	D-Threitol, 2,3-*O*-(2,2,2-trichloroethylidene)-, dimethanesulfonate											85

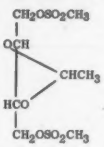


90074	65403	Erythritol, 2,3-*O*-(2,2,2-trichloroethylidene)-, dimethanesulfonate											122

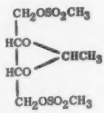


90075	66343	L-Threitol, 2,3-*O*-ethylidene-, dimethanesulfonate											>100

90076	66344	D-Threitol, 2-3-*O*-ethylidene-, dimethanesulfonate											>100



90077	66345	Erythritol, 2,3-*O*-ethylidene-, dimethanesulfonate											>100



90078	67128	L-Threitol, 2,3-cyclic carbonate, dimethanesulfonate											7.2

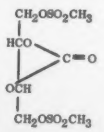


TABLE 3.—Group 6: three- and four-carbon sugar methanesulfonates without nitrogen—Continued

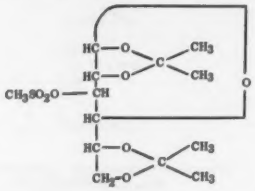
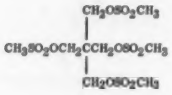
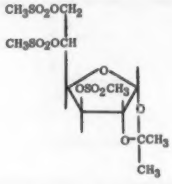
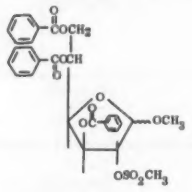
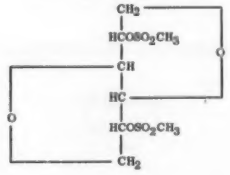
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED_{50}
90079	67129	L-Threitol, 1,4-dimethanesulfonate cyclic sulfite											9.3
90080	67130	L-Threitol, 2,3-bis(ethyl carbonate) 1,4-dimethanesulfonate											>100
90081	72473	L-Threitol, 2,3-*O*-(2,2,2-trifluoroethylidene)-, dimethanesulfonate											>100
90082	75820	1,2,4-Butanetriol, 1,4-dimethanesulfonate											>100
90083	76303	DL-Glycerol, 1,3-dimethanesulfonate											7.8
90084	82399	L-1,2,4-Butanetriol, 1,4-dimethanesulfonate					400†	85					96

†Only dose tested.

TABLE 3.—Group 6: three- and four-carbon sugar methanesulfonates without nitrogen—Continued

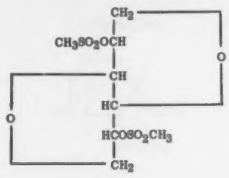
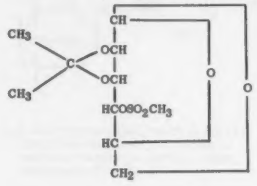
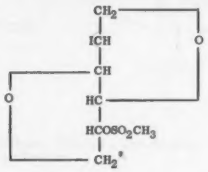
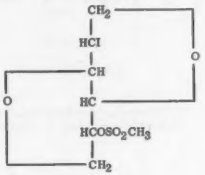
Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90085	87907	L-Threitol, 2,3-bis(hydrogen sulfate) 1,4-dimethanesulfonate, disodium salt											11
90086	88191	DL-threo-2,3-Butanediol, 1,4-bis-(benzyloxy)-, dimethanesulfonate											29
90087	94160	Erythritol, 1,4-dimethanesulfonate											>100
90088	98767	DL-Threitol, 1,4-dimethanesulfonate			300	59							

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED_{50}
90089	14162	D-Glucofuranose, 1,2:5,6-di-*O*-isopropylidene-, methanesulfonate	500†	0			175†	0	(250,500*)	0			
													
90090	31720	Methanesulfonic acid, tetraester with pentaerythritol	400†	0			400†	0	500†	26			
													
90091	33261	D-Glucofuranose, 1,2-*O*-isopropylidene-, trimethanesulfonate	450†	0			200	32	500†	41			>100
													
90092	33267	D-Glucofuranoside, methyl, 2,5,6-tribenzoate 2-methanesulfonate	338†	0					375†	33			
													
90093	33694	D-Sorbitol, 1,4:3,6-dianhydro-, dimethanesulfonate	100†	0	200	10	100†	0	125†	0			
													

*Toxic dose.
†Only dose tested.

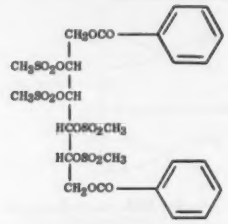
TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90094	33695	D-Mannitol, 1,4:3,6-dianhydro-, dimethanesulfonate	400†	0	400†	43	400†	84	500†	21			
													
90095	33696	β-D-Mannopyranose, 1,6-anhydro-2,3-O-isopropylidene-, methanesulfonate	112†	0			112†	0	125†	0			>100
													
90096	33697	D-Mannitol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-, methanesulfonate	88†	4			88†	0	125†	0			
													
90097	33698	D-Sorbitol, 1,4:3,6-dianhydro-2(or 5)-deoxy-2(or 5)-iodo-, methanesulfonate	112†	0			112†	0	125†	0			
													

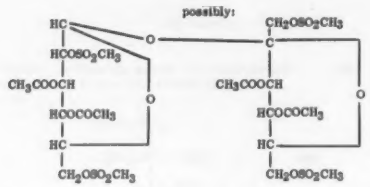
†Only dose tested.

TABLE 8.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

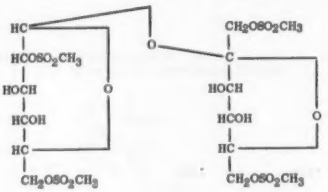
Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90098	33699	D-Mannitol, 1,6-dibenzoate 2,3,4,5-tetramethanesulfonate	100†	0					125†	0			



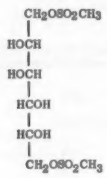
90099	34439	Sucrose, tetraacetate tetramethanesulfonate	450†	0			450†	0	500†	2			



90100	34532	Sucrose, tetramethanesulfonate											>100

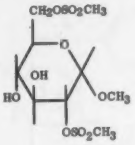
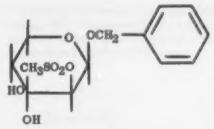
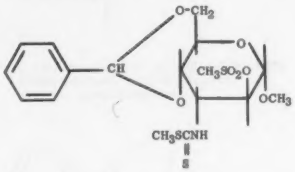
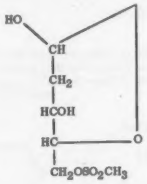
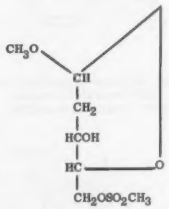


90101	37538	Mannitol, 1,6-dimethanesulfonate, D-	112†	4	500	94	113†	20	(125,500*)	0	200	43	10



*Toxic dose.
†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90102	39114	α-D-Glucopyranoside, methyl, 2,6-bis(methanesulfonate)	400†	15	400†	24							
													
90103	39268	β-D-Arabinopyranoside, benzyl, 2-methanesulfonate	450†	0			450†	21	500†	12			
													
90104	52400	α-D-Altropyranoside, methyl 4,6-*O*-benzylidene-3-deoxy-3-[(dithiocarboxy)amino]-, methyl ester, methanesulfonate	400†	0			400†	0	500†	46			
													
90105	62796	D-Ribose, 2-deoxy-, 5-methanesulfonate					(25,75,225)	0					46
													
90106	62797	β-D-Ribofuranoside, methyl 2-deoxy-, 5-methanesulfonate					(25,75,225)	0					30
													

†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90107	62798	β-D-Ribofuranoside, methyl 2-deoxy-, dimethanesulfonate					(25,75,225)	0					>100
90108	62799	β-D-Ribofuranoside, benzyl 2-deoxy-, 5-methanesulfonate					(25,75,225)	0					>100
90109	69435	α-D-Galactopyranoside, methyl, 4-methanesulfonate	400†	0			500†	7					>100
90110	72392	D-glycero-D-gluco-Heptitol, 1,3:2,3:-5,7-tri-*O*-benzylidene-, methanesulfonate											>100

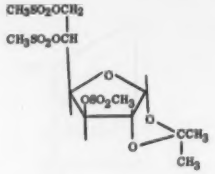
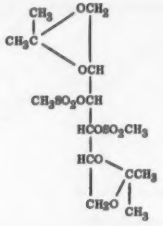
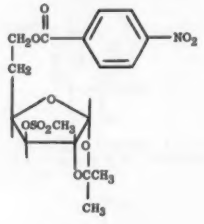
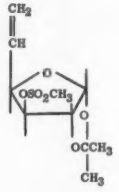
†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90111	72559	α-D-Galactopyranoside, methyl, 2,3,6- tribenzoate 4-methanesulfonate	(100,200*)	0					250†	19	200†	42	49
90112	73269	α-D-Arabinofuranoside, methyl 3-deoxy-3-[(dithiocarboxy)amino]-, methyl ester, 2-methanesulfonate 5-(methyl carbonate)	200†	0					250†	0	200	6†	25
90113	75751	α-D-Altropyranoside, methyl 4,6-*O*-benzylidene-3-(cyanoamino)-3-deoxy-, methanesulfonate											27
90114	75752	α-D-Altropyranoside, methyl 3-(benzylcyanoamino)-4,6-*O*-benzylidene-3-deoxy, methanesulfonate											26
90115	76348	α-D-Arabinofuranoside, methyl 3-amino-3-deoxy-5-thio-, 2-methanesulfonate, hydrochloride											>100

*Toxic dose.
†Only dose tested.

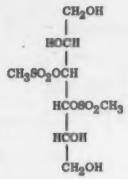
TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90116	76349	α-D-Glucofuranose, 1,2-*O*-isopropylidene-, 3,5,6-trimethanesulfonate	175†	0					250†	13	175†	34	>100
													
90117	78789	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-, dimethanesulfonate	400†	0					500†	0			>100
													
90118	79247	D-Glucofuranose, 5-deoxy-1,2-*O*-isopropylidene-, 3-methanesulfonate, 6-*p*-nitrobenzoate	(100,200*)	0					250†	25	200†	10	30
													
90119	79488	α-D-xylo-Hexos-5-ene, 5,6-dideoxy-1,2-*O*-isopropylidene-, methanesulfonate (furo[2,3-*d*]-1,3- dioxol-6-ol, 2,2-dimethyl-5-vinyl-, methanesulfonate)	200†	0					250†	0	200†	0	32
													

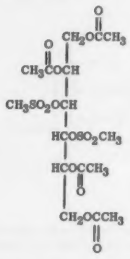
*Toxic dose.
†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

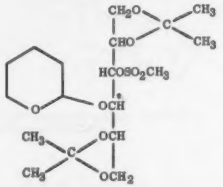
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90120	80604	D-Mannitol, 3,4-dimethanesulfonate											>100



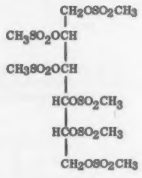
90121	80605	D-Mannitol, 1,2,5,6-tetraacetate 3,4-dimethanesulfonate											>100



90122	80730	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-4-*O*-(tetrahydropyran-2-yl)-, methanesulfonate	(125,500*)	0									>100



90123	81989	D-Mannitol, hexamethanesulfonate											>100

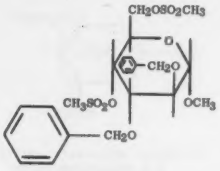
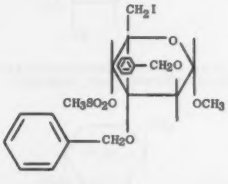
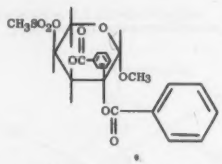
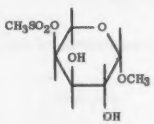
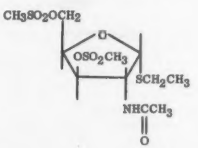


*Toxic dose.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

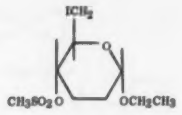
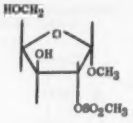
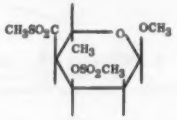
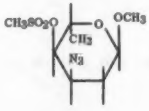
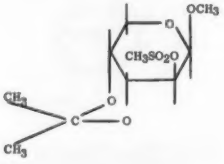
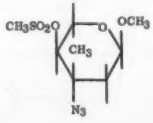
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90124	83062	D-Mannitol, 1,2:5,6-di-*O*-isopropylidene-, 4-benzoate 3-methanesulfonate											>100
90125	83404	L-Iditol, 1,4:3,6-dianhydro-, dimethanesulfonate											36
90126	83405	D-Glucitol, 1,4:3,6-dianhydro-5-deoxy-5-(dimethylamino)-, methanesulfonate, hydrochloride											>100
90127	83636	*myo*-Inositol, 1,4,5,6-tetramethanesulfonate											111
90128	92318	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-, methanesulfonate											28

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90129	92319	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-, dimethanesulfonate											31
													
90130	92320	α-D-Altropyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-, methanesulfonate											28
													
90131	92712	β-L-Arabinopyranoside, methyl, 2,3-dibenzoate 4-methanesulfonate	400†	0			400†	0	500†	0			51
													
90132	92714	β-L-Arabinopyranoside, methyl, 4-methanesulfonate	400†	0			400†	19	500†	0			>100
													
90133	100054	α-D-Xylofuranoside, ethyl 2-acetamido-2-deoxy-1-thio-, 3,5-dimethanesulfonate	255†	0									
													

†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		I.L		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90134	105411	α-D-*erythro*-Hexopyranoside, ethyl 2,3,6-trideoxy-6-iodo-, methanesulfonate											>100
													
90135	106760	α-D-Xylofuranoside, methyl, 2-methanesulfonate	400†	5	400†	10							
													
90136	107401	α-L-*arabino*-Hexopyranoside, methyl 2,6-dideoxy-, dimethanesulfonate	300†	0	300†	0							
													
90137	108083	L-*ribo*-Hexopyranoside, methyl 3-azido-2,3,6-trideoxy-, 4-methanesulfonate, α-											100
													
90138	108084	Arabinopyranoside, methyl 3,4-*O*-isopropylidene-, methanesulfonate, β-D-	400†	12	400†	0							
													
90139	109522	L-*arabino*-Hexopyranoside, methyl 3-azido-2,3,6-trideoxy-, 4-methanesulfonate, α-	400†	11									
													

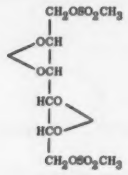
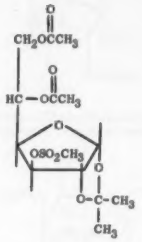
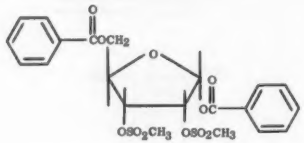
†Only dose tested.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90140	111709	Xylopyranoside, methyl 3-acetamido-3-deoxy-, dimethanesulfonate (ester), L-	400‡	10									
90141	112864	Arabinopyranoside, methyl, 2-methanesulfonate, β-D-	400†	6									
90142	113472	Arabinopyranoside, methyl 3,4-di-*O*-methyl-, methanesulfonate, β-D-	100‡	6									
90143	114012	Galactitol, 2,4:3,5-di-*O*-isopropylidene-, dimethanesulfonate, D-	100‡	4	100†	0							
90144	117359	Galactitol, 1,6-dimethanesulfonate, D-	400†	8									

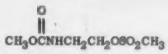
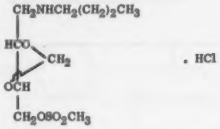
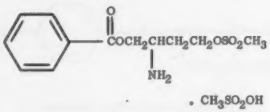
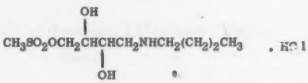
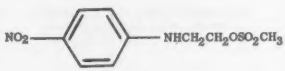
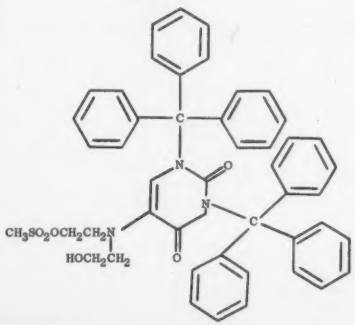
†Only dose tested.
‡Single treatment.

TABLE 3.—Group 7: five- and six-carbon sugar methanesulfonates without nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90145	122801	Mannitol, 2,3:4,5-di-*O*-methylene-, dimethanesulfonate, D-	400†	0									
													
90146	400288	D-Glucose, 1,2-*O*-isopropylidene-, 5,6-diacetate, 3-methanesulfonate											>100
													
90147	400293	α-D-Ribose, 1,3,5-tribenzoate, 2-methanesulfonate											80
													

†Only dose tested.

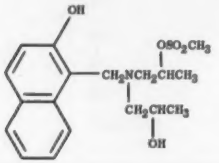
TABLE 3.—Group 8: monomethanesulfonates with nitrogen

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90148	44342	Carbamic acid, (2-hydroxyethyl)-, methyl ester, methanesulfonate	450†	0			450†	42	500†	28			
													
90149	70310	L-Threitol, 1-(butylamino)-1-deoxy-2,3-*O*-methylene-, methanesulfonate, hydrochloride (1,3-dioxolane-4-methanol, 5-[(butylamino)methyl]-, methanesulfonate, hydrochloride)											>100
													
90150	80585	1,4-Butanediol, 2-amino-, 1-benzoate 4-methanesulfonate, methanesulfonate (salt)											>100
													
90151	80897	*threo*-1,2,3-Butanetriol, 4-(butylamino)-, 1-methanesulfonate, hydrochloride											>100
													
90152	100773	Ethanol, 2-(*p*-nitroanilino)-, methanesulfonate (ester)	100	19									2.4
													
90153	101761	Uracil, 5-[bis(2-hydroxyethyl)-amino]1,3-ditrityl-, 5-methanesulfonate (ester)	100§	5									
													

†Only dose tested.
§Single treatment.

TABLE 3.—Group 8: monomethanesulfonates with nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90154	109265	2-Propanol, 1,1'-[[(2-hydroxy-1-naphthyl) methyl]imino]di-, 2-methanesulfonate	400†	0	50–400	0							



†Only dose tested.

TABLE 3.—Group 9: dimethanesulfonates with nitrogen

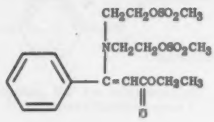
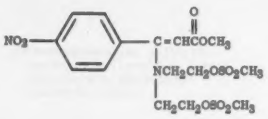
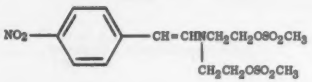
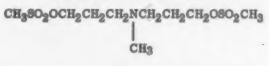
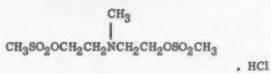
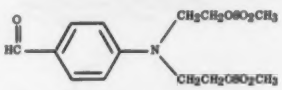
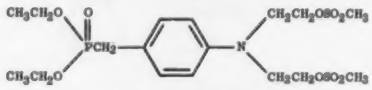
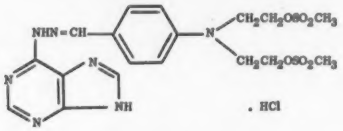
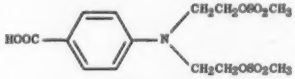
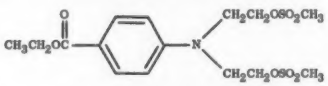
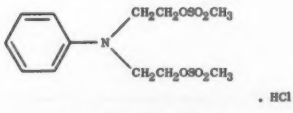
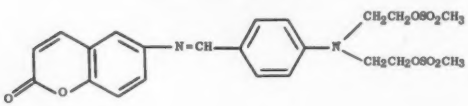
Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90155	71088	Cinnamic acid, β-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate											28
													
90156	72602	Cinnamic acid, β-[bis(2-hydroxyethyl)amino]-p-nitro-, methyl ester, dimethanesulfonate											13
													
90157	72603	Ethanol, 2,2′-(p-nitrostyrylimino)di-, dimethanesulfonate											16
													
90158	84641	1-Propanol, 3,3′-(methylimino)di-, dimethanesulfonate, hydrochloride	65	166	not tested								
													
90159	102627	1-Propanol, 3,3′-iminodi-, dimethanesulfonate (ester), hydrochloride	36	143									47
90160	115485	Ethanol, 2,2′-(methylimino)di-, dimethanesulfonate (ester), hydrochloride	0.2	40	0.75	61							
													

TABLE 3.—Group 10: *N*-aryl dimethanesulfonates with nitrogen

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90161	24820	Benzaldehyde, *p*-[bis(2-hydroxyethyl)amino]-, dimethanesulfonate	8.0†	19	4.0	92							
													
90162	27401	Phosphonic acid, (*p*-[bis(2-hydroxyethyl)amino]benzyl)-, diethyl ester, dimethanesulfonate	65†	15									
													
90163	54012	Benzaldehyde, *p*-[bis(2-hydroxyethyl)amino]-, purin-6-ylhydrazone, dimethanesulfonate ester, hydrochloride	50	37	200	93							
													
90164	59640	Benzoic acid, *p*-[bis(2-hydroxyethyl)amino]-, dimethanesulfonate (ester)	66	22	100	93							
													
90165	59643	Benzoic acid, *p*-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate (ester)	25	23	200	95							
													
90166	71035	Ethanol, 2,2'-(phenylimino)di-, dimethanesulfonate, hydrochloride	22	0	11	82							
													
90167	72151	Coumarin, 6-[[*p*-[bis(2-hydroxyethyl)amino]benzylidene]amino]-, dimethanesulfonate (ester)	24	48	96	96							
													

†Only dose tested.

TABLE 3.—Group 10: *N*-aryl dimethanesulfonates with nitrogen—Continued

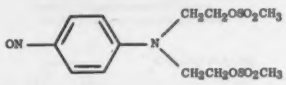
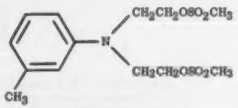
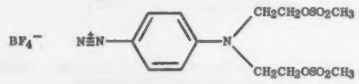
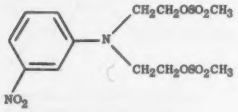
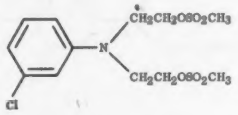
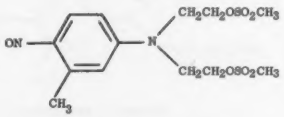
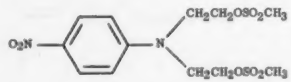
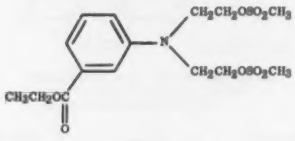
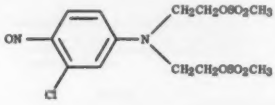
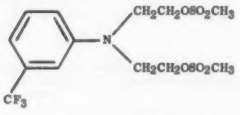
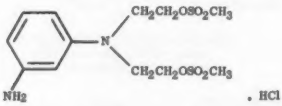
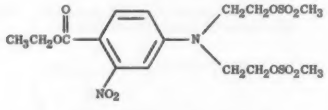
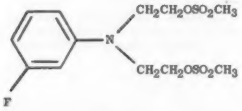
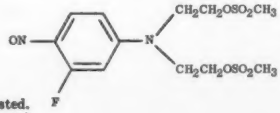
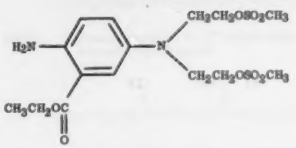
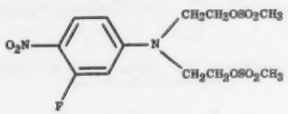
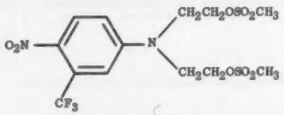
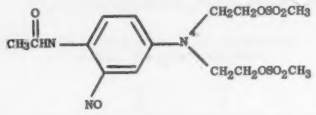
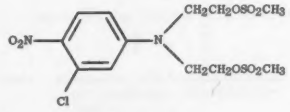
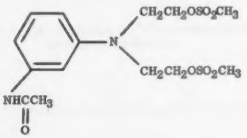
Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90168	79423	Ethanol, 2,2′-[(*p*-nitrosophenyl)-imino]di-, dimethanesulfonate	0.32	35	1.0	86							<0.1
													
90169	82276	Ethanol, 2,2′-(*m*-tolylimino)di-, dimethanesulfonate (ester)											51
													
90170	82361	Benzenediazonium, *p*-[bis(2-hydroxyethyl)amino]-, tetrafluoroborate, dimethanesulfonate (ester)	1.25	57	2.5	97							2.1
													
90171	100774	Ethanol, 2,2′-[(*m*-nitrophenyl)-imino]di-, dimethanesulfonate (ester)	100	48	45	95							6.8
													
90172	101671	Ethanol, 2,2′-[(*m*-chlorophenyl)-imino]di-, dimethanesulfonate (ester)	16	38									
													
90173	101672	Ethanol, 2,2′-[(4-nitroso-*m*-tolyl)imino]di-, dimethanesulfonate (ester)	0.5	32									
													
90174	101673	Ethane, 2,2′-[(*p*-nitrophenyl)-imino]di-, dimethanesulfonate (ester)	50	15									
													

TABLE 3.—Group 10: *N*-aryl dimethanesulfonates with nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED60
90175	101674	Benzoic acid, *m*-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate (ester)	32	18	32	94							
													
90176	102467	Ethanol, 2,2′-[(3-chloro-4-nitrosophenyl)imino]di-, dimethanesulfonate	38	31									
													
90177	102468	Ethanol, 2,2′-[(*α*,*α*,*α*-trifluoro-*m*-toyl)imino]di-, dimethanesulfonate	38	27	17	100							
													
90178	102469	Ethanol, 2,2′-[(*m*-aminophenyl)imino]di-, dimethanesulfonate, monohydrochloride	3.6§	40									
													
90179	103362	Benzoic acid, 5-[bis(2-hydroxyethyl)amino]-2-nitro, ethyl ester, dimethanesulfonate	400†	4	400†	21							1.7
													
90180	103363	Ethanol, 2,2′-[(*m*-fluorophenyl)imino]di-, dimethanesulfonate	20§	28									0.15
													
90181	103961	Ethanol, 2,2′-[(3-fluoro-4-nitrosophenyl)imino]di-, dimethanesulfonate (ester)	5†	41	5†	88							0.013
													

†Only dose tested.
§Single treatment.

TABLE 3.—Group 10: *N*-aryl dimethanesulfonates with nitrogen—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90182	103962	Benzoic acid, 2-amino-5-[bis(2-hydroxyethyl)amino]-, ethyl ester, dimethanesulfonate (ester), monohydrochloride	5	36	1.25	82							6.0
		 . HCl											
90183	104962	Ethanol, 2,2′-[(3-fluoro-4-nitrophenyl)imino]di-, dimethanesulfonate (ester)	200§	15									6.2
													
90184	104963	Ethanol, 2,2′-[(α,α,α-trifluoro-4-nitro-*m*-tolyl)imino]di-, dimethanesulfonate (ester)	400†	0	400†	toxic							16
													
90185	104964	Acetanilide, 3′-[bis(2-hydroxyethyl)amino]-6′-nitroso-, dimethanesulfonate (ester)	0.1	23	3.4	83							0.018
													
90186	104965	Ethanol, 2,2′-[(3-chloro-4-nitrophenyl)imino]di-, dimethanesulfonate (ester)	400†	25	50†	75							6.7
													
90187	104967	Acetanilide, 3′-[bis(2-hydroxyethyl)amino]-, dimethanesulfonate (ester)	2.0	68	5.0	95							8.9
													

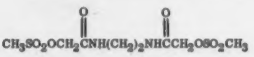
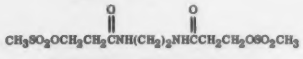
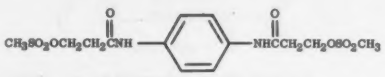
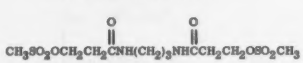
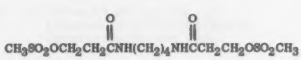
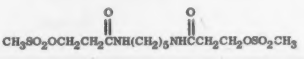
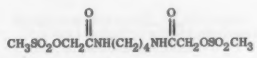
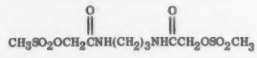
†Only dose tested.
§Single treatment.

TABLE 3.—Group 11: piperazine dimethanesulfonates

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90188	47774	Piperazine, 1,4-dihydracryloyl-, dimethanesulfonate; piposulfan	50	62	25	95	44	82	100	35	100	54	
90189	53577	Piperazine, 1,4-diglycoloyl-, dimethanesulfonate	75†	0			25	37	80†	18			
90190	57845	Piperazine, 1,4-bis(2-methylhydracryloyl)-, dimethanesulfonate	225†	21			225	31	250†	42			
90191	61147	Piperazine, 1,4-dihydracryloyl-*trans*-2,5-dimethyl-, dimethanesulfonate	135	65	32	96	75	80	125	39			
90192	61152	Piperazine, 1,4-bis(2,2-dimethylhydracryloyl)-, dimethanesulfonate	4.7¶	6			9.4	40	3.9	28			

†Only dose tested.
¶Next highest dose (18.8 mg/kg) was toxic.

TABLE 3.—Group 12: diamine dimethanesulfonates

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90193	24901	Glycolamide, *N,N′*-ethylene-bis-, dimethanesulfonate	400	45	200	77	95	91	40	39	200	18	
													
90194	53582	Hydracrylamide, *N,N′*-ethylenebis-, dimethanesulfonate	35†	18			40	88	125	50			<1.0
													
90195	55104	Hydracrylamide, *N,N′*-*p*-phenylene-bis-, dimethanesulfonate					183	15					
													
90196	55109	Hydracrylamide, *N,N′*-trimethylene-bis-, dimethanesulfonate	56†	14	100†	90	56	75	62†	13			2.3
													
90197	55110	Hydracrylamide, *N,N′*-tetramethyl-enebis-, dimethanesulfonate	225†	14			225	80	225†	28			
													
90198	55111	Hydracrylamide, *N,N′*-pentamethyl-enebis-, dimethanesulfonate	225†	12			225	75	250†	36			14
													
90199	55112	Hydracrylamide, *N,N′*-hexamethyl-enebis-, dimethanesulfonate	225†	15	225†	45	250†	2					150
90200	57844	Hydracrylamide, *N,N′*-methylene-bis-, dimethanesulfonate	36	43	62‡	95	28	79	30†	50			17
90201	58805	Acetamide, *N,N′*-tetramethylene-bis[2-hydroxy-, dimethanesulfonate											21
													
90202	58825	Glycolamide, *N,N′*-trimethylenebis-, dimethanesulfonate	75	55			35†	37					
													

†Only dose tested.
‡Single treatment. OD > LD10.

TABLE 3.—Group 12: diamine dimethanesulfonates—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED90
90203	61151	Hydracrylamide, *N,N'*-propylene-bis-, dimethanesulfonate	113	41	50	92	56	68	160†	51			
		$CH_3SO_2OCH_2CH_2\overset{\overset{O}{\|}}{C}NHCH\overset{\overset{CH_3}{\|}}{C}H_2NH\overset{\overset{O}{\|}}{C}CH_2CH_2OSO_2CH_3$											
90204	61154	Hydracrylamide, *N,N'*-(2-methyltrimethylene) bis-, dimethanesulfonate	450†	24			200	95	500	46			38
		$CH_3SO_2OCH_2CH_2\overset{\overset{O}{\|}}{C}NHCH_2\overset{\overset{CH_3}{\|}}{C}HCH_2NH\overset{\overset{O}{\|}}{C}CH_2CH_2OSO_2CH_3$											
90205	97877	Glycolamide, *N,N'*-(2-hydroxytrimethylene) bis-, dimethanesulfonate (ester)											83
		$CH_3SO_2OCH_2\overset{\overset{O}{\|}}{C}NHCH_2\overset{\overset{OH}{\|}}{C}HCH_2NH\overset{\overset{O}{\|}}{C}CH_2OSO_2CH_3$											
90206	106625	Ethanol, 2,2'-[tetramethylenebis(methylimino)]di-, dimethanesulfonate (ester), monohydrochloride	1.7	63	3.0	85							
		$CH_3SO_2OCH_2CH_2\overset{\overset{CH_3}{\|}}{N}(CH_2)_4\overset{\overset{CH_3}{\|}}{N}CH_2CH_2OSO_2CH_3$											
90207	122402	Erythritol, 1,4-dideoxy-1,4-bis[(2-hydroxyethyl)amino]-, 1,4-dimethanesulfonate (ester), meso-	10	130									
		$CH_2NHCH_2CH_2OSO_2CH_3$ $\|$ $HCOH$ $\|$ $HCOH$ $\|$ $CH_2NHCH_2CH_2OSO_2CH_3$											

†Only dose tested.

TABLE 3.—Group 13: aminobutanediols methanesulfonates

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90208	80277	Benzamide, *N*-[3-hydroxy-1-(hydroxymethyl)propyl]-, dimethanesulfonate											>100
90209	80989	Benzamide, *N,N'*-[DL-1,2-bis(hydroxymethyl)ethylene]bis-, dimethanesulfonate											91
90210	82856	DL-2,3-Butanediol, 1,4-bis(dimethylamino)-, dimethanesulfonate, dihydrochloride											>100
90211	83951	DL-*threo*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)											18
90212	85624	L-*threo*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)											25
90213	85625	*erythro*-2,3-Butanediol, 1,4-diamino-, dimethanesulfonate, dimethanesulfonate (salt)											12
90214	91300	Methanesulfonamide, *N,N'*-[*meso*-1,2-bis(hydroxymethyl)ethylene]-bis-, dimethanesulfonate											45

TABLE 3.—Group 13: aminobutanediols methanesulfonates—Continued

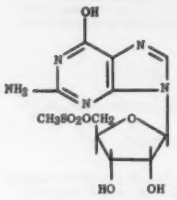
Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90215	92133	**Methanesulfonamide, *N,N'*-(*meso*-2,3-dihydroxytetramethylene) bis-, dimethanesulfonate; methanesulfonic acid, *meso*-1,2-bis(methanesulfonamidomethyl) ethylene ester**											7.4
90216	92952	**Methanesulfonamide, *N,N'*-(DL-2,3-dihydroxytetramethylene) bis-, dimethanesulfonate**											29
90217	92953	**Methanesulfonamide, *N,N'*-(D-2,3-dihydroxytetramethylene) bis-, dimethanesulfonate**											21
90218	93100	**Methanesulfonamide, *N,N'*-[DL-1,2-bis(hydroxymethyl) ethylene] bis-, dimethanesulfonate**											24
90219	93101	**p-Toluenesulfonamide, *N,N'*-(*meso*-2,3-dihydroxytetramethylene) bis-, dimethanesulfonate**											27
90220	93651	**Carbamic acid, [D-1,2-bis(hydroxymethyl) ethylene] di-, diethyl ester, dimethanesulfonate**											5.5
90221	94021	**1,2,5-Thiadiazolidine-DL-*trans*-3,4-dimethanol, 2,5-bis(methylsulfonyl)-, dimethanesulfonate, 1-oxide**											16

TABLE 3.—Group 13: aminobutanediols methanesulfonates—Continued

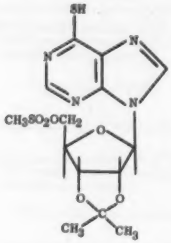
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90222	94748	Carbamic acid, (L-2,3-dihydroxytetramethylene) di-, diethyl ester, dimethanesulfonate											>100
90223	94749	Carbamic acid, [DL-1,2-bis(hydroxymethyl) ethylene]di-, diethyl ester, dimethanesulfonate											120

TABLE 3.—Group 14: nucleoside methanesulfonates

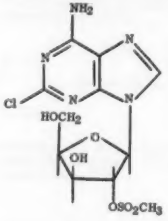
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90224	62627	Guanosine, 5′-methanesulfonate					60	45					>100



90225	76466	9*H*-purine-6-thiol, 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-, 5′-methanesulfonate											>100



90226	80100	Adenine, 2-chloro-9-β-D-xylofuranosyl-, 2′-methanesulfonate											>100



90227	82218	Adenine, 9-(3,5-anhydro-β-D-xylofuranosyl)-, 2′-methanesulfonate											33

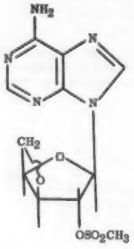


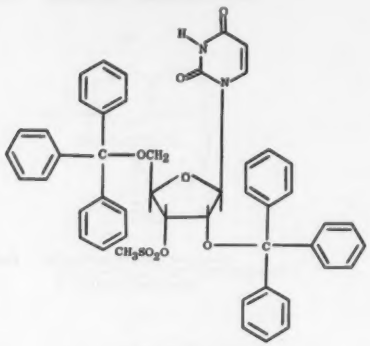
TABLE 3.—Group 14: nucleoside methanesulfonates—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90228	83215	Uracil, 1-β-D-arabinofuranosyl-, 5′-benzoate 3′-methanesulfonate	400†	0					500†	0	400†	31	>100
90229	88792	6*H*-furo[2′,3′ :4,5]oxazolo[3,2-*a*]-pyrimidin-6-one, 2,3,3a,9a-tetrahydro-3-hydroxy-2-(hydroxymethyl)-, 2-benzoate 3-methanesulfonate											25
90230	90841	Adenine, 2-chloro-9-(3,5-*O*-isopropylidene-β-D-xylofuranosyl-, 2′-methanesulfonate	250†	0					250†	0	250†	39	78

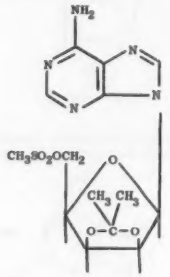
†Only dose tested.

TABLE 3.—Group 14: nucleoside methanesulfonates—Continued

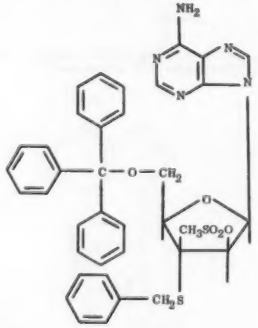
Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90231	94675	Uridine, 2',5'-di-*O*-trityl-, 3'-methanesulfonate	400†	0					500†	24	400†	0	62



90232	97114	Adenine, 9-(2,3-*O*-isopropylidene-β-D-lyxofuranosyl)-, 5'-methanesulfonate	>100



90233	97115	Adenine, 9-(3-*S*-benzyl-3-thio-5-*O*-trityl-β-D-arabinofuranosyl)-, 2'-methanesulfonate	21



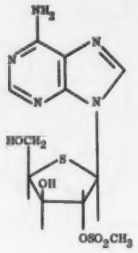
†Only dose tested.

Entry No.	NSC No.	Compound name	L1210 OD	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
90234	101158	Adenine, 9-(3-*S*-benzyl-3-thio-β-D-arabinofuranosyl)-, 2′-methanesulfonate											48
90235	106754	Adenine, 9-(3,5-*O*-isopropylidene-4-thio-β-D-xylofuranosyl)-, 2′-methanesulfonate	400†§	0									
90236	107184	Adenine, 9-[3-deoxy-3-[(dithiocarboxy)amino]-5-*O*-trityl-β-L-arabinofuranosyl]-*N*-trityl-, methyl ester, 2′-methanesulfonate	200†§	0									

†Only dose tested.
‡Single treatment. OD > LD10.

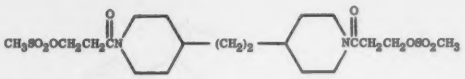
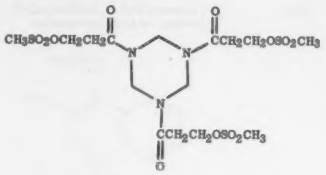
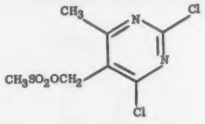
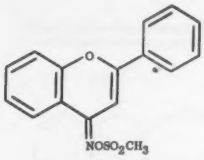
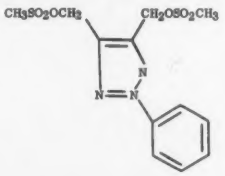
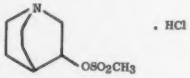
TABLE 3.—Group 14: nucleoside methanesulfonates—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90237	107400	Adenine, 9-(4-thio-β-D-xylofuranosyl)-, 2'-methanesulfonate	300†§	0									



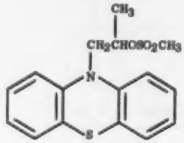
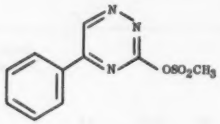
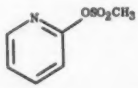
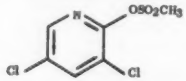
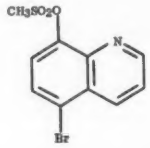
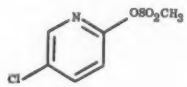
†Only dose tested.
§Single treatment.

TABLE 3.—Group 15: miscellaneous compounds containing methanesulfonates

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90238	53581	Piperidine, 4,4′-ethylenebis[1-hydracryloyl-, dimethanesulfonate	(113,225*)	0			75	29	250†	18			
													
90239	57847	s-Triazine, 1,3,5-trihydracryloyl-hexahydro-, trimethanesulfonate	225†	7			225	19	250†	19			
													
90240	62570	5-Pyrimidinemethanol, 2,4-dichloro-6-methyl-, methanesulfonate	3.0	3			7.0†	29	8.0	14			2.9
													
90241	69567	Flavone, *o*-(methylsulfonyl)oxime	11†	9					16	41			
													
90242	77394	1*H*-1,2,3-triazole-4,5-dimethanol, 1-phenyl-, dimethanesulfonate (methanesulfonic acid, [(1-phenyl-1*H*-1,2,3-triazole-4,5-diyl)-dimethylene]ester)											>100
													
90243	79422	3-Quinuclidinol, methanesulfonate, hydrochloride	5	4									26
		 . HCl											

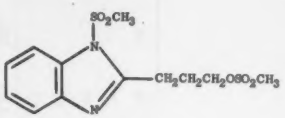
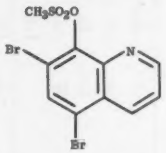
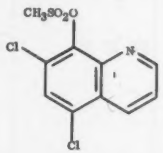
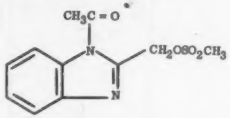
†Only dose tested.

TABLE 8.—Group 15: miscellaneous compounds containing methanesulfonates—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90244	97892	Phenothiazine-10-ethanol, α-methyl-, methanesulfonate											22
													
90245	98981	as-Triazin-3-ol, 5-phenyl-, methanesulfonate (ester)											86
													
90246	110559	2-Pyridinol, methanesulfonate (ester)	50†	7	50†	37							
													
90247	110561	2-Pyridinol, 3,5-dichloro-, methanesulfonate (ester)	150	0	300†	49							
													
90248	110562	8-Quinolinol, 5-bromo-, methanesulfonate (ester)	100†	1	100†	22							
													
90249	110563	2-Pyridinol, 5-chloro-, methanesulfonate (ester)	25	6	25†	20							
													

†Only dose tested.

TABLE 3.—Group 15: miscellaneous compounds containing methanesulfonates—Continued

Entry No.	NSC No.	Compound name	L1210		W-256		CA-755		S-180		LL		KB
			OD	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
90250	110676	2-Benzimidazolepropanol, 1-(methylsulfonyl)-, methanesulfonate (ester)	(100,200)‡	10	320†	0							
													
90251	110905	8-Quinolinol, 5,7-dibromo-, methanesulfonate (ester)	400†	0									
													
90252	110906	8-Quinolinol, 5,7-dichloro-, methanesulfonate (ester)	400†	0									
													
90253	112898	2-Benzimidazolemethanol, 1-acetyl-, methanesulfonate (ester)	50†	0									
													

†Only dose tested.
‡Single treatment.

TABLE 4.—Structure-activity relationships of active compounds: alkyl methanesulfonates without nitrogen*

$CH_3SO_2O–R$

NSC No.	Entry No.	R	L1210		W-256		CA-755		S-180		KB
			OD†	ILS	OD	TWI	OD	TWI	OD	TWI	ED50
3718	89977	–H			(50–400‡)	0					
50256	89988	$–CH_3$	50	10	100	95	50	12			28
26805	89983	$–CH_2CH_3$	140§	8	140§	62			(125,500‡)	0	>100
52142	89989	$–CH_2CH_2F$	100¶	45**			8.0	43			>100
18016	89979	$–CH_2CH_2Cl$	75	2	100	70	140	79	53	7	>100
49551	89986	$–CH_2CH_2Br$	60	7	25	24	60§	2	65	15	100
26358	89982	$–CH_2CH_2CN$	450§	0					500§	5	
49872	89987	$–CH_2CH_2CH_3$	400	18	400	58§	(175–350‡)	0	500§	46	
49507	89985	$–(CH_2)_2CH_2Cl$	110§	0			55	13	125	6	
67176	89990	$–CH_2(CH_2)_2CH_2Cl$	400§	20	200	92					
106788	89993	$–CH_2C(Br)=CHBr$	150§	8	150§	87					

*See table 3, group 1.
†OD = optimal dose, mg/kg.
‡Toxic dose.
§Only dose tested.
¶Single treatment; OD > LD50.
**Underlined values indicate activity.

TABLE 5.—Structure-activity relationships of active compounds: two methanesulfonates without nitrogen*

$CH_3SO_2O–R–OSO_2CH_3$

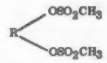
NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
17016	90038	$-(CH_2)_2-$	170‡	0					170‡	0			
17017	90039	$-(CH_2)_3-$	170	7			30	75	57	47			100
750	90036	$-(CH_2)_4-$	12.5	17	26	80	40	50	39	40			20
17019	90040	$-(CH_2)_5-$	25	15	25	95	12.5	50	50	60			24
3052	90037	$-(CH_2)_6-$	108	31§	100	83	16	74	62.5	30	50	50	

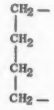
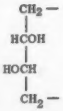
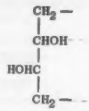
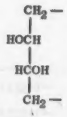
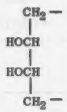
$R'SO_2O–(CH_2)_4OSO_2R'$

NSC No.	Entry No.	R'	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
750	90036	CH_3-	12.5	17	26	80	40	50	39	40			20
106308	90059	$ClCH_2-$			150	91							

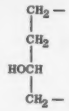
*See table 3, group 5.
†OD = optimal dose, mg/kg.
‡Only dose tested.
§Underlined values indicate activity.

TABLE 6.—Structure-activity relationships of active compounds: four-carbon sugar methanesulfonates without nitrogen compared with busulfan (NSC-750)*



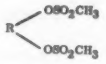
NSC No.	Entry No.	R	L1210		W-256		CA-755		S-180		LL		KB
			OD†	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
750	90036		12.5	17	26	80‡	40	50	39	40			29
39069	90068		1000	32	1600	96	500	94					
98767	90088				300	59							
39068	90068										1000	45	3.0
39070	90069		200§	0			200§	0	250§	7	62.5	29	5.4

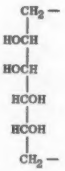
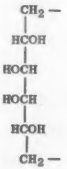
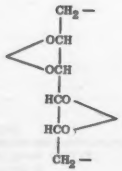
82399	90084		400§	85	96

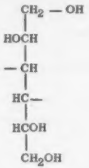


*See table 3, group 6.
†OD = optimal dose, mg/kg.
‡Underlined values indicate activity.
§Only dose tested.

TABLE 7.—Structure-activity relationships of active compounds: six-carbon sugar methanesulfonates without nitrogen*

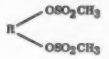


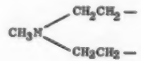
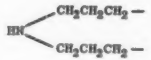
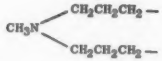
NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
37538	90101		112‡	4	500	94§	113‡	20	(125,500¶)	0	200	43	10
117359	90144		400‡	3									
122801	90145		400‡	0									

80604	90120		>100

*See table 3, group 7.
†OD = optimal dose, mg/kg.
‡Only dose tested.
§Underlined values indicate activity.
¶Toxic dose.

TABLE 8.—Structure-activity relationships of active compounds: dimethanesulfonates with nitrogen*

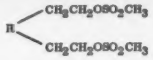


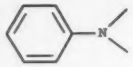
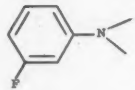
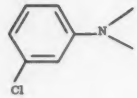
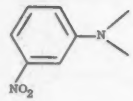
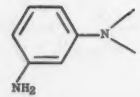
NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	KB ED50
115485	90160		0.2	40‡	0.75	61	
102627	90159		36	143			47
84641	90158		65	166			

*See table 3, group 9.
†OD = optimal dose, mg/kg.
‡Underlined values indicate activity.

TABLE 9.—Structure-activity relationships of active compounds: *N*-aryl dimethanesulfonates with nitrogen*

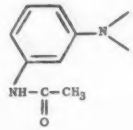
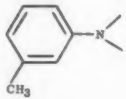
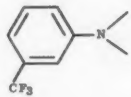
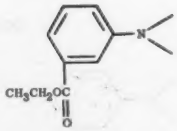
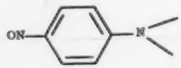
TABLE 9.—Structure-activity relationships of active compounds: *N*-aryl dimethanesulfonates with nitrogen*

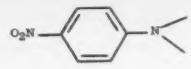
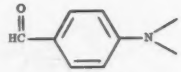
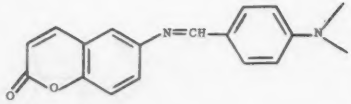
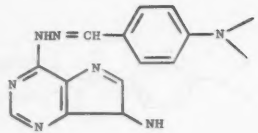


NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	KB ED50
71035	90166		22	0	11	82	
103363	90180		20‡	28§			0.15
101671	90172		16	38			
100774	90171		100	48	45	95	6.8
102469	90178		3.6‡	40			

*See table 3, group 10.
†OD = optimal dose, mg/kg.
‡Single treatment.
§Underlined values indicate activity.

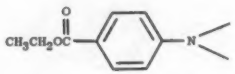
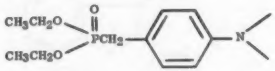
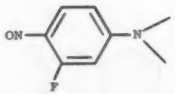
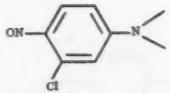
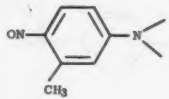
TABLE 9.—Structure-activity relationships of active compounds: *N*-aryl dimethanesulfonates with nitrogen*—Continued

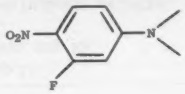
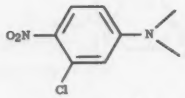
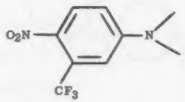
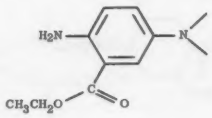
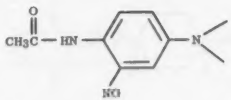
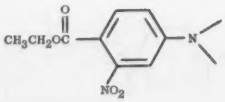
NSC No.	Entry No.	R	L1210		W-256		KB
			OD†	ILS	OD	TWI	ED50
104967	90187		2.0	68	5.0	95	8.9
82276	90169						51
102468	90177		38	27	17	100	
101674	90175		32	18	32	94	
79423	90168		0.32	35	1.0	86	<0.1
			50	15			

101673	90174		50	15			
82361	90170		1.25	57	2.5	97	2.1
24820	90161		8.0¶	19	4.0	92	
72151	90167		24	48	96	96	
54012	90163		50	37	200	93	
59640	90164		66	22	100	93	

*See table 3, group 10.
†OD = optimal dose, mg/kg.
¶Only dose tested.

TABLE 9.—Structure-activity relationships of active compounds: *N*-aryl dimethanesulfonates with nitrogen*—Continued

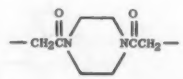
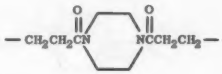
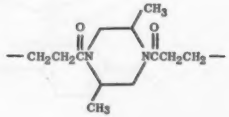
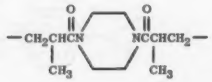
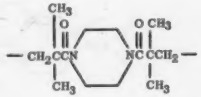
NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	KB ED50
59643	90165		25	23	200	95	
27401	90162		65¶	15			
103961	90181		5¶	41	5¶	88	0.013
102467	90176		38	31			
101672	90173		0.5	32			

104962	90183		200‡	15			6.2
104965	90186		400¶	25	50¶	75	6.7
104963	90184		400¶	0	400¶	toxic	16
103962	90182		5	36	1.25	82	6.0
104964	90185		0.1	23	3.4	83	0.018
103362	90179		400¶	4	400¶	21	1.7

*See table 3, group 10.
†OD = optimal dose, mg/kg.
‡Single treatment.
§Underlined values indicate activity.
¶Only dose tested.

TABLE 10.—Structure-activity relationships of active compounds: piperazine dimethanesulfonates*

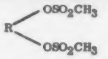
$CH_3SO_2O–R–OSO_2CH_3$

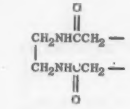
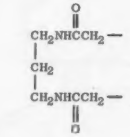
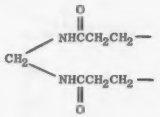
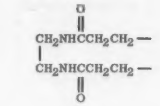
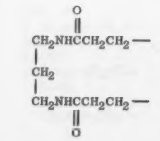
NSC No.	Entry No.	R	L1210		W-256		CA-755		S-180		LL	
			OD†	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI
53577	90189		75‡	0			25	37	80‡	18		
47774	90188		50	62§	25	95	44	82	100	35	100	54
61147	90191		135	65	32	96	75	80	125	39		
57845	90190		225‡	21			225	31	250‡	42		
61152	90192		4.7¶	6			9.4	40	3.9	28		

*See table 3, group 11.
†OD = optimal dose, mg/kg.
‡Only dose tested.
§Underlined values indicate activity.
¶Next highest dose (18.8 mg/kg) was toxic.

TABLE 11.—Structure-activity relationships of active compounds: diamine dimethanesulfonates*

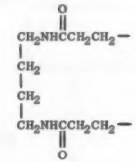
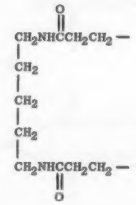
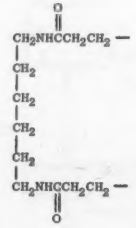
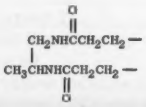
TABLE 11.—Structure-activity relationships of active compounds: diamine dimethanesulfonates*

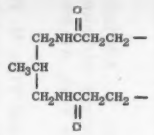
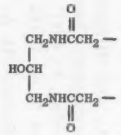
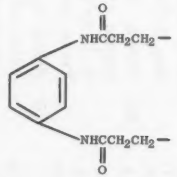
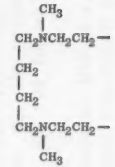
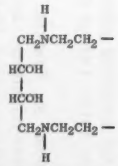


NSC No.	Entry No.	R	L1210		W-256		CA-755		S-180		LL		KB
			OD†	ILS	OD	TWI	OD	TWI	OD	TWI	OD	TWI	ED50
24901	90193		400	45‡	200	77	95	91	40	39	200	18	
58825	90202		75	55			35§	37					
57844	90200		36	43	62¶	95	28	79	30§	50			17
53582	90194		35§	18			40	88	125	50			<1.0
55109	90196		56§	14	100§	90	56	75	62§	13			2.3

*See table 3, group 12.
†OD = optimal dose, mg/kg.
‡Underlined values indicate activity.
§Only dose tested.
¶Single treatment. OD > LD50.

TABLE 11.—Structure-activity relationships of active compounds: diamine dimethanesulfonates*—Continued

NSC No.	Entry No.	R	L1210 OD†	L1210 ILS	W-256 OD	W-256 TWI	CA-755 OD	CA-755 TWI	S-180 OD	S-180 TWI	LL OD	LL TWI	KB ED50
55110	90197		225§	14			225	80	225§	28			
55111	90198		255§	12			225	75	250§	36			14
55112	90199		225§	15	225§	45	250§	2					150
61151	90203		113	41	50	92	56	68	160§	51			
61154	90204		450§	24			200	25	500	46			25

61154	90204		450§	24			200	95	500	48	25
97877	90205										83
55104	90195						183	15			
106625	90235		1.7	63	3.0	85					
122402	90207		10	130							

*See table 3, group 12.
†OD = optimal dose, mg/kg.
‡Underlined values indicate activity.
§Only dose tested.
¶Single treatment. OD >LD50.

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Effect of Compounds on a Spectrum of Rat Tumors [1,2]

Kanematsu Sugiura, Franz A. Schmid, Miyono M. Schmid, and George F. Brown [3,4]

SUMMARY

Two hundred and fifty-seven compounds were tested for antitumor effects against the Flexner-Jobling rat carcinoma, 323 against the Walker rat carcinosarcoma 256, 270 against the Jensen rat sarcoma, 54 against the mitomycin C-resistant Jensen rat sarcoma, 44 against the rat sarcoma R39, 40 against the Yoshida rat sarcoma, 52 against the Moore rat sarcoma No. 1, 252 against the Murphy-Sturm rat lymphosarcoma, 33 against the rat fibrosarcoma No. 1, 13 against the rat fibrosarcoma No. 4, 18 against the rat fibrosarcoma No. 6, 20 against the rat fibrosarcoma No. 7, 76 against the Babcock rat kidney tumor, 42 against the Novikoff rat hepatoma, 84 against the Iglesias functional rat ovarian tumor, 60 against the Iglesias rat sarcoma, and 58 against the Iglesias functional rat adrenal tumor. Of the alkylating agents studied, cyclophosphamide (NSC-26271; SK-20501) was the most effective against the spectrum of tumors studied, followed by 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; NSC-409962; SK-27702) (1-7), L-sarcolysin (NSC-8806; SK-15673), and tris(1-aziridinyl)phosphine sulfide (NSC-6396; SK-6882) (8) respectively. Of the pyrimidine analogs, 2,4-bis(1-aziridinyl)-6-chloropyrimidine (NSC-48225; SK-4383) appeared to be most effective, followed by 2′-deoxy-5-fluorocytidine (NSC-48006; SK-20000) and 5-fluorouracil (5-FU; NSC-19893; SK-18143) (9). 6-Mercaptopurine (6-MP; NSC-755; SK-5357) had the best antitumor effect among the purine analogs tested, followed by pseudourea, 2-purin-6-yl-2-thio, hydrochloride (NSC-526485; SK-26485). The antimetabolite methotrexate (NSC-740; SK-1275) (10) appeared to be the most effective of this group of agents, followed by aminopterin (NSC-739; SK-1072) (11). Hydrocortisone (NSC-10483E; SK-3047) was the most active steroid among 18 steroids tested. Of the 65 antibiotics, mitomycin C (NSC-26980; SK-19256) had the strongest antitumor activity. 2-Ethyl-4-nitroquinoline 1-oxide (SK-16293) (9) had a moderately inhibitory effect against Walker carcinosarcoma 256 and Murphy-Sturm lymphosarcoma, but 12 other quinolines were inactive against a spectrum of rat tumors. Of the 149 miscellaneous compounds tested, the following seven compounds had a strong or completely inhibitory effect against one to three tumors: hydracrylamide, *N,N′*-ethylenebis-, dimethanesulfonate (NSC-53582; SK-25513); propionamide, *N,N′*-ethylenebis[3-bromo]- (NSC-49403; SK-25512); acrylamide, *N*-[(3-bromopropionamido)methyl]- (NSC-66248; SK-26071); 7-hydroxy-9α-methoxymitosane (SK-28239); urethane

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[3] Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, New York, NY.

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(NSC-746; SK-129); indole-3-propionic acid, hydrazide (NSC-25649); SK-8856); and L-asparaginase (NSC-109229; SK-30000). The study showed that it was possible to cause permanent and complete regression of certain well-established 7-day-old tumors with compounds given at the maximum tolerated dose. Animals with 7-day-old tumors responded to the agents as well as animals with 1-day-old tumors.

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The search for effective drugs for a particular form of cancer requires the testing of large numbers of compounds against many types of tumors. At Sloan-Kettering Institute for Cancer Research, many synthetic compounds and natural products have been screened during the past 20 years using a spectrum of 40 transplantable mouse, rat, hamster, and chicken tumors.

This report consists of observations on the effects of 375 compounds on the growth of 17 transplantable rat tumors. The compounds are classified as alkylating agents, pyrimidine analogs, purine analogs, antimetabolites, steroids, antibiotics, quinoline analogs, and miscellaneous agents.

MATERIALS AND METHODS

The tumors used in the present study were (*a*) the Flexner-Jobling rat carcinoma (FRC), a spontaneous tumor which arose in the seminal vesicle; (*b*) the Walker rat carcinosarcoma 256 (W256), a spontaneous tumor which arose in the mammary gland; (*c*) the Jensen rat sarcoma (JRS), a spontaneous tumor; (*d*) mitomycin C-resistant Jensen rat sarcoma (JRS-MC-resistant), produced from JRS; (*e*) the rat sarcoma R39 (R39), a spontaneous tumor; (*f*) the Yoshida rat sarcoma (YRS), produced by feeding *O*-aminoazotoluene; (*g*) the Moore rat sarcoma No. 1 (MRS No. 1), which arose from a human embryonic rhabdomyosarcoma grown in tissue culture and subsequently transplanted into rats; (*h*) the Murphy-Sturm rat lymphosarcoma (MRLS), produced by 1,2,5,6-dibenzathracene; (*i*) the rat fibrosarcomas Nos. 1, 4, 6, 7 (RFS Nos. 1, 4, 6, 7), induced by 3-hydroxyxanthine; (*j*) the Babcock rat kidney tumor (BRK), a spontaneous tumor; (*k*) Novikoff rat hepatoma (NRH), induced by feeding 4-dimethylaminoazobenzene; (*l*) Iglesias functional rat ovarian tumor (FOT), a spontaneous tumor; (*m*) Iglesias rat sarcoma (OT), transformed from FOT; and (*n*) Iglesias functional rat adrenal tumor (AT), a spontaneous tumor. The history, biologic properties, and cytologic description of these tumors have been presented elsewhere (12).

Small pieces of tumor, each weighing approximately 8 mg, were implanted subcutaneously (sc) into young adult, healthy male and female rats (Wistar strain, 80–100 g initial body weight; Carworth Farms, New City, NY), except for JRS, YRS, and NRH when Sprague-Dawley rats were used (Blue Spruce Farms, Altamont, NY), and FOT, OT, and AT when A x C rats were used (Bark-Ridge Farms, Wenonak, NJ). A single implant was made by trocar into the right axillary region. These rat tumors "take" in 100% of the transplant attempts, with low average tumor regression rates except in four rat tumors, FRC, JRS, YRS, and NRH, where 13%, 17%, 15%, and 50% spontaneous tumor regressions occur respectively.

Tumor-bearing animals were divided into two groups, one group of ten for controls and one of five for treatment. The animals were maintained on a standard diet (Purina Laboratory Chow) and water ad libitum.

Solutions or suspensions of compounds were prepared with saline (S), carboxymethylcellulose (CMC), peanut oil (PO), gum acacia (GA), alcohol and saline (A+S), alcohol and water (A+W), alcohol and carboxymethylcellulose (A+C), alcohol and peanut oil (A+P), butyl succinate (BS), or propylene glycol (PG). The compounds were injected intraperitoneally (ip) (except for steroids, which were given sc) when tumors were 24 hours old and the injections were continued for 7 successive days. The usual injection volume was 0.5 ml once daily. The extent of inhibition of growth of the solid tumors was graded 2 weeks after treatment began. However, in the case of FOT and AT the inhibition of tumor growth was determined 4 and 8 weeks later because these

tumors grew very slowly. In some instances when established tumors were used, treatment was started on the seventh day and the inhibition of tumor growth was determined 2 weeks later. The criteria for evaluating tumor inhibition are given in table 1.

Table A lists the chemical names, the Sloan-Kettering (SK) numbers, the NSC numbers, the CAS registry numbers, the molecular formulas, and the code numbers of the sources. The compounds will be referred to in tables 2–19 by their NSC and SK numbers.

RESULTS

The effects of compounds given at or near the maximum tolerated dose (MTD) are presented in table 2 for FRC, in table 3 for W256, in table 4 for JRS, in table 5 for JRS-MC-resistant in table 6 for R39, in table 7 for YRS, in table 8 for MRS No. 1, in table 9 for MRLS, in table 10 for RFS No. 1, in table 11 for RFS No. 4, in table 12 for RFS No. 6, in table 13 for RFS No. 7, in table 14 for BRK, in table 15 for NRH, in table 16 for FOT, in Table 17 for OT, and in table 18 for AT. The agents were given at or near the chronic MTD (seven daily injections), ie, the dose at which at least 60% of the animals survived. A twofold increase in this dose would kill at least 60% of all animals. A few of the compounds were tested at doses higher than well-tolerated levels. The data are averages of the results of multiple experiments for positive results. Current data on some antitumor agents previously shown to be effective are included in the tables because previous studies were either preliminary or because some additional experiments were performed with chemically related compounds.

Flexner-Jobling Rat Carcinoma (FRC)

It is clear that FRC is very sensitive to alkylating agents (13–15). Among 43 compounds tested, 32 (74%) had a strong or completely inhibitory effect on FRC. Cyclophosphamide (NSC-26271; SK-20501) (16) at a dose of 25 mg/kg/day caused complete destruction of the tumor. A dose of 6.25 mg/kg/day, one fourth the MTD, had a completely inhibitory effect. L-Sarcolysin (NSC-8806; SK-15673) (17) at a dose of 1.0 mg/kg/day had a completely inhibitory effect on FRC. The antitumor effects of *N*-formylsarcolysyl derivatives of glycine (NSC-525691; SK-25691), alanine (NSC-526622; SK-26622), valine (NSC-526406; SK-26406), and glutamic acid (NSC-527453; SK-27453); of *N*-acetylsarcolysyl derivatives of glycine (NSC-526407; SK-26407), alanine (NSC-525823; SK-25823), and valine (NSC-525022; SK–25022); and of sarcoylsin hexyl ester (SK-20597) are essentially the same as those of L-sarcolysin. Tris(1-aziridinyl)phosphine sulfide (NSC-6396; SK-6882) at doses of 4.0, 2.0, or 1.0 mg/kg/day caused complete destruction of the tumor. At a dose of 0.5 mg/kg/day the compound produced a moderately inhibitory effect on FRC.

1,9-Nonanediol, dimethanesulfonate (NSC-3052; SK-7505) (18) at a dose of 100 mg/kg/day had a completely inhibitory effect on FRC, but 1,4-butanediol, dimethanesulfonate (NSC-750; SK-5681) at a dose of 5.0 mg/kg/day had a moderately inhibitory effect.

The antitumor actions of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; NSC-409962; SK-27702) (19), 1-methyl-1-nitrosourea (NSC-23909; SK-24464), and hydroxyurea (NSC-32065; SK-22591) against FRC were compared. BCNU, the most effective, produced complete inhibition of tumor growth with a dose of 8.0 mg/kg/day. At a dose of 4.0 mg/kg/day it gave a strong inhibition and at 2.0 mg/kg/day it gave a slight inhibition. 1-Methyl-1-nitrosourea at a dose of 20 mg/kg/day produced a strong inhibition but hydroxyurea at a dose of 100 mg/kg/day had no inhibitory effect on FRC.

Diethylamine, 2,2′-dichloro-*N*-methyl-, *N*-oxide, compd. with hydrochloride (1:1) (NSC-10107; SK-598); 5-[bis(2-chloroethyl)amino]-, DL-tryptophan (NSC-62403; SK-27456); 1,4-bis(2-bromopropionyl)piperazine (NSC-41269; SK-11088); phosphinic acid, bis(1-aziridinyl)-, *p*-phenylene ester (NSC-42158; SK-17360); and 2,4,6-tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) also had a completely inhibitory effect on FRC.

The alkylating agents *N*-phenylsulfonyl-*P,P,P*-tris(1-aziridinyl)phosphineimide (NSC-520644; SK-20644); *N*-(*p*-toluenesulfonyl)-*P,P,P*-tris(1-aziridinyl)phosphineimide (NSC-520645; SK-20645); *N*-(*p*-methoxyphenylsulfonyl)-*P,P,P*-tris(1-aziridinyl)phosphineimide (NSC-520646; SK-20646); and *N*-(*p*-chlorophenylsulfonyl)-*P,P,P*-tris(1-aziridinyl)phos-

phineimide (NSC-520647; SK-20647) had a strong to completely inhibitory effect on FRC.

FRC is apparently not sensitive to pyrimidines. Among 14 compounds tested, one (7%) had a strong inhibitory effect on FRC. 2′-Deoxy-5-fluorocytidine (NSC-48006; SK-20000) at a dose of 10 or 25 mg/kg/day had a strong inhibitory effect; 5-fluorouracil (5-FU; NSC-19893; SK-18143) at a dose of 25 mg/kg/day had a moderately inhibitory effect.

Among 35 purine analogs tested, five (14%) had a strong inhibitory effect on FRC. These compounds are pseudourea, 2-purine-6-yl-2-thio-, hydrochloride (NSC-526485; SK-26485); 6-mercaptopurine (6-MP; NSC-755; SK-5357) (20); azathioprine (NSC-39084; SK-20354); thiocyanic acid, purin-6-yl ester (NSC-58385; SK-14377); and 6-mercaptopurine riboside (NSC-4911; SK-12355).

FRC is resistant to antimetabolites. All of the 11 antimetabolites tested, including methotrexate (NSC-740; SK-1272), had no inhibitory effect on this tumor.

Of the 14 steroids tested against FRC, only prednisolone, 9-fluoro-, 21-acetate (NSC-12600E; SK-15347) had a moderately inhibitory effect; all other steroids were uniformly inactive.

Of the 51 antibiotics tested against FRC, only mitomycin C (NSC-26980; SK-19256) (21) and its six derivatives, methyl mitomycin C (SK-20779), 1*a*-acetylmitomycin C (SK-28008), 1*a*-propionylmitomycin C (SK-28009), 1*a*-butroylmitomycin C (SK-28010), 1*a*-benzoylmitomycin C (SK-28146), and 1*a*-chloroacetylmitomycin C (SK-28242), had a strong or completely inhibitory effect on FRC; the other 45 antibiotics (88%) had only a slight or no effect.

All of the six quinoline analogs tested against FRC were inactive.

Of the 86 miscellaneous compounds tested against FRC only *N*-[(3-bromopropionamido) methyl]acrylamide (NSC-66248; SK-26071); *N,N′*-ethylenebishydracrylamide, dimethanesulfonate (NSC-53582; SK-25513); and indole-3-propionic acid, hydrazide (NSC-25649; SK-8856) had a strong or completely inhibitory effect on FRC. Vincristine (NSC-67574; SK-26327) and urethane (NSC-746; SK-129) had a moderately inhibitory effect; the remaining 81 compounds (94%) had a slight or no inhibitory effect.

Walker Carcinosarcoma 256 (W256)

It is clear that W256 is very sensitive to alkylating agents. Among 55 compounds tested, 35 (64%) had a strong or completely inhibitory effect. 2,4,6-Tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133), at a dose of 0.5 or 0.25 mg/kg/day, and tris(1-aziridinyl)phosphine sulfide (NSC-6396; SK-6882), at a dose of 2.0 mg/kg/day, caused complete destruction of the tumor. Cyclophosphamide (NSC-26271; SK-20501) at a dose of 25, 12.5, or 6.25 mg/kg/day had a strong inhibitory effect on the tumor. BCNU (NSC-409962; SK-27702) at a dose of 8.0, 4.0, or 2.0 mg/kg/day had a strong inhibitory effect on this tumor, and at 1.0 mg/kg/day it had a moderately inhibitory effect. Ethylene glycol, dimethanesulfonate (NSC-17016; SK-6699); 1,4-butanediol, dimethanesulfonate (NSC-750; SK-5681); and 1,9-nonanediol, dimethanesulfonate (NSC-3052; SK-7505) (18) had equally strong inhibitory effects on W256. Twenty-four other alkylating agents, namely, mechlorethamine (NSC-762; SK-101), NSC-9506 (SK-1424), L-sarcolysin (NSC-8806; SK-15673), merphalan (NSC-14210; SK-21739), sarcolysin amyl ester (SK-20598), sarcolysin hexyl ester (SK-20597), *N*-formylsarcolysyl derivative of glycine (NSC-525691; SK-25691), NSC-526407 (SK-26407), NSC-525823 (SK-25823), NSC-525022 (SK-25022), NSC-527453 (SK-27453), NSC-62403 (SK-27456), NSC-46338 (SK-14913), NSC-34462 (SK-19849), NSC-84641 (SK-29102), NSC-49421 (SK-4614), NSC-9717 (SK-3818), NSC-520644 (SK-20644), NSC-520645 (SK-20645), NSC-520647 (SK-20647), NSC-42158 (SK-17360), SK-15385, NSC-26806 (SK-22595), SK-2732, NSC-528988 (SK-28988), and NSC-48225 (SK-4383) had a strong inhibitory effect on W256.

Of the 18 pyrimidine analogs tested against W256, none had a strong inhibitory effect. 5-FU (NSC-19893; SK-18143) and 16 other pyrimidines were only slightly inhibitory or had no effect on W256.

Among 36 purine analogs tested against W256, none had a strong or completely inhibitory effect. 6-MP (NSC-755; SK-5357), 6-mercaptopurine 3-oxide (NSC-528013; SK-28013), and 9*β*-D-ribofuranosyl-9*H*-purine-6-

thiol (NSC-4911; SK-12355) had moderately inhibitory effects, but the other 33 compounds showed slight inhibition or no effect.

Among 12 antimetabolites (22) tested against W256, methotrexate (NSC-740; SK-1275) and SK-1833 had moderately inhibitory effects; the other ten compounds were slightly inhibitory or showed no effect. Among 14 steroids tested against W256, hydrocortisone (NSC-10483E; SK-3047) caused a moderate inhibition; other steroids had slight inhibition or no effect.

Among 58 antibiotics tested against W256, mitomycin C (NSC-26980; SK-19256) and its five derivatives, 1*a*-acetylmitomycin C (SK-28008), 1*a*-propionylmitomycin C (SK-28009), 1*a*-butroylmitomycin C (SK-28010), 1*a*-benzoylmitomycin C (SK-28146), and 1*a*-chloroacetylmitomycin C (SK-28242), had strong inhibitory effects, while methyl mitomycin C (SK-20779) and 1*a*-*p*-toluenesulfonylmitomycin C (SK-28145) had almost no inhibitory effect on this tumor. The other 50 antibiotics tested against W256 were ineffective.

2-Ethyl-4-nitroquinoline 1-oxide (SK-16293) had a moderately inhibitory effect on W256, but 12 other quinoline analogs were inactive.

Crystalline L-asparaginase (NSC-109229; SK-30000) (23) at a dose of 5000 IU/kg/day caused a strong inhibitory effect on W256. 1-Hydroxy-2-amino-7-aminomitosane (SK-28265) also had a strong inhibitory effect, while hexamethylmelamine (NSC-13875; SK-1905); 2-(ethylamino)-1,3,4-thiadiazole (NSC-4730; SK-14406); *N,N'*-ethylenebishydracrylamide, dimethanesulfonate (NSC-53582; SK-25513); *N,N'*-ethylenebis[3-bromo]propionamide (NSC-49403; SK-25512); and 2,3-bis(methylthio)-1,4-naphthoquinone (NSC-523486; SK-23486) had a moderately inhibitory effect on W256. None of the other 109 miscellaneous compounds tested had more than a slight effect.

Jensen Rat Sarcoma (JRS)

It is clear that JRS is very sensitive to alkylating agents (18). Among 48 compounds tested, 30 (63%) had a completely inhibitory effect, and eight (17%) had a strong inhibitory effect. Diethylamino, 2,2'-dichloro-*N*-methyl-, *N*-oxide compd. with hydrochloride (1:1) (nitromin) (NSC-10107; SK-598) at a dose of 1.5, 0.75, or 0.5 mg/kg/day caused complete destruction of JRS. The *N*-formyl-sarcolysyl derivative of valine (NSC-525022; SK-25022) at a dose of 100 or 50 mg/kg/day had a completely inhibitory effect on this tumor. BCNU (NSC-409962; SK-27702) at a dose of 8.0 or 4.0 mg/kg/day caused complete destruction of JRS. However, 1-methyl-1-nitrosourea (NSC-23909; SK-24464) had no inhibitory effect. Cyclophosphamide (NSC-26271; SK-20501) appeared to be the most effective compound. JRS was completely destroyed by one half, one fourth, and one eighth of the MTD of 50 mg/kg/day. Similarly, tris(1-aziridinyl)phosphine sulfide (NSC-6396; SK-6882) at a dose of 4.0, 2.0, 1.0, or 0.5 mg/kg/day caused complete inhibition.

Of the 12 pyrimidine analogs tested only 2'-deoxy-5-fluorouridine (NSC-27640; SK-19150) had a moderately inhibitory effect on JRS; all other pyrimidines tested had no activity.

Among 29 purine analogs tested against JRS, 2-purin-6-yl-2-thiopseudourea, hydrochloride (NSC-526485; SK-26485) and 2-amino-6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine (NSC-38887; SK-20355) had a moderately inhibitory effect. 6-MP (NSC-755; SK-5357) had no inhibitory effect on this tumor.

Among 11 antimetabolites tested against JRS, aminopterin (NSC-739; SK-1072) and methotrexate (NSC-740; SK-1275) gave a strong or completely inhibitory effect; the others were essentially negative.

All of the 12 steroids tested against JRS, including cortisone (NSC-49420E; SK-2795), had no inhibitory effect.

Among 52 antibiotics tested against JRS, ten (19%) had a strong or completely inhibitory effect on this tumor. Mitomycin C (NSC-26980; SK-19256) at a dose of 1.0 or 0.5 mg/kg/day caused complete destruction of the tumor; at a dose of 0.25 mg/kg/day it had a strong inhibitory effect. Six derivatives of mitomycin C, methyl mitomycin C (SK-20779), 1*a*-acetylmitomycin C (SK-28008), 1*a*-propionylmitomycin C (SK-28009), 1*a*-butroylmitomycin C (SK-28010), 1*a*-benzoylmitomycin C (SK-28146), and 1*a*-chloroacetylmitomycin C (SK-28242), had a completely inhibitory effect. Fumagillin (NSC-9168; SK-6258) (24), mitomycin D (NSC-524678; SK-24678), and porfiromycin (NSC-56410; SK-25021) had a strong or completely inhibitory effect. The remaining 42 antibiotics had a moderate, a slight, or no inhibitory effect.

All of the ten quinoline analogs tested against JRS were inactive.

Of the 98 miscellaneous compounds tested against JRS only *N*-[(3-bromopropionamido)-methyl]acrylamide (NSC-66248; SK-26071); hydracrylamide, *N,N'*-ethylenebis-, dimethanesulfonate (NSC-53582; SK-25513); propionamide, *N,N'*-ethylenebis[3-bromo]- (NSC-49403; SK-25512); 7-hydroxy-9α-methoxymitosane (SK-28239); mannitol, 1,6-dimethanesulfonate, D- (NSC-37538; SK-21569); and an arginine polymer (NSC-524784; SK-24784) had a strong or completely inhibitory effect on the tumor. Four compounds had a moderately inhibitory effect, and the remaining 88 compounds (90%) had a slight or no inhibitory effect.

Mitomycin C-Resistant Jensen Sarcoma (JRS-MC-Resistant)

A total of 54 compounds and antibiotics were tested against a mitomycin C-resistant JRS (25). Twenty-five compounds which were effective against the mitomycin C-sensitive JRS were found to be relatively non-inhibitory against the mitomycin C-resistant JRS: 15 alkylating agents (NSC-762 [SK-101], NSC-8806 [SK-15673], NSC-525691 [SK-25691], NSC-526407 [SK-26407], NSC-525823 [SK-25823], NSC-526622 [SK-26622], NSC-525022 [SK-25022], NSC-526406 [SK-26406], NSC-527453 [SK-27453], NSC-527456 [SK-27456], NSC-47774 [SK-24591], NSC-3052 [SK-7505], NSC-26271 [SK-20501], NSC-9706 [SK-1133], and NSC-6396 [SK-6882]); one pyrimidine (NSC-27640; SK-19150); one purine (NSC-526485; SK-26485); two folic acid antagonists (NSC-739 [SK-1072] and NSC-740 [SK-1275]); three antibiotics (NSC-26980 [SK-19256], SK-20779, and NSC-56410 [SK-25021]); four miscellaneous compounds (NSC-66248 [SK-26071], NSC-53582 [SK-25513], NSC-49403 [SK-25512], and NSC-524784 [SK-24784]). Twenty-eight compounds which were inactive or slightly inhibitory against the mitomycin C-sensitive sarcoma were judged to be relatively inactive against mitomycin C-resistant sarcoma.

Rat Sarcoma R39 (R39)

It is evident from table 6 that R39 is very sensitive to alkylating agents. Eight out of eight compounds tested (100%) had a strong or completely inhibitory effect on this tumor. 2,4,6-Tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) at a dose of 5.0, 2.5, 1.0, 0.5, or 0.1 mg/kg/day caused complete inhibition of R39.

2,4-Bis(1-aziridinyl)-6-chloropyrimidine (NSC-48225; SK-4383) at a dose of 1.5, 1.0, or 0.5 mg/kg/day had a completely inhibitory effect on R39 but had no effect at a dose of 0.25 mg/kg/day.

Among four purine analogs tested, 6-MP (NSC-755; SK-5357) at a dose of 50 mg/kg/day had a strong inhibitory effect on R39; 2,6-diaminopurine, monohydrate (NSC-743; SK-1395) had no activity.

Of the seven antimetabolites tested against R39, aminopterin (NSC-739; SK-1072) (11) and methotrexate (NSC-740; SK-1272) had a moderately inhibitory effect on this tumor, while amino-an-fol (SK-1332), diopterin (SK-1718), and teropterin (SK-860) had no effect.

Cortisone, 21-acetate (NSC-49420E; SK-2795) (26) had a moderately inhibitory effect on R39.

Six antibiotics had no effect on R39: penicillin G (NSC-402815; SK-2405); streptomycin, sulfate (NSC-14083; SK-4516); chloramphenicol (NSC-3069; SK-2155); chlorotetracycline (NSC-13252; SK-1333); terramycin, hydrochloride (NSC-9169; SK-2859); and borrelidin (SK-2935).

Urethane (NSC-746; SK-129) at a dose of 100 mg/kg/day had a moderately inhibitory effect on R39 with some toxicity.

Yoshida Rat Sarcoma (YRS)

It is clear that YRS is very sensitive to alkylating agents. Among 17 compounds tested, 15 (88%) had a completely inhibitory effect, one had a strong inhibitory effect, and one had a moderately inhibitory effect on YRS. 5-[Bis-(2-chloroethyl)amino]-DL-tryptophan (NSC-62403; SK-27456) at a dose of 1.0 or 0.5 mg/kg/day had a completely inhibitory effect on YRS. BCNU (NSC-409962; SK-27702) at a dose of 8.0, 4.0, or 2.0 mg/kg/day produced complete inhibition of tumor growth, while 1-methyl-1-nitrosourea (NSC-23909; SK-24464) had a moderately inhibitory effect. 2,4,6-Tris-(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) at a dose of 0.125 mg/kg/day caused complete inhibition of the tumor.

Although the number of compounds tested in each group was small, pyrimidines, purines, antimetabolites, steroids, quinolines, and miscel-

laneous compounds had essentially no inhibitory effect on YRS. Mitomycin C (NSC-26980; SK-19256) and its derivatives, 1*a*-butroylmitomycin C (SK-28010), 1*a*-benzoylmitomycin C (SK-28146), and 1*a*-chloroacetylmitomycin C (SK-28242), had a completely inhibitory effect on YRS while 1*a*-*p*-toluenesulfonylmitomycin C (SK-28145), chromomycin A_3 (NSC-58514; SK-20863), and iyomycin B_1, hydrochloride (NSC-83340; SK-28487) had no activity.

Moore Rat Sarcoma No. 1 (MRS No. 1)

It is evident from table 8 that MRS No. 1 is very sensitive to alkylating agents. Among 13 compounds tested, 11 (85%) had a strong inhibitory effect on MRS No. 1. L-Sarcolysin (NSC-8806; SK-15673) and its *N*-formylsarcolysyl derivative of glycine (NSC-525691; SK-25691), of alanine (NSC-525823; SK-25823), of valine (NSC-525022; SK-25022), and of glutamic acid (NSC-527453; SK-27453); and the acetylsarcolysyl derivative of glycine (NSC-526407; SK-26407), of alanine (NSC-526622; SK-26622), and of valine (NSC-526406; SK-26406) had a strong inhibitory effect on MRS No. 1. 2,4,6-Tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) at a dose of 0.25, 0.125, 0.0625, or 0.0312 mg/kg/day had a strong inhibitory effect on MRS No. 1. Pyrimidines, purines, antimetabolites, and steroids had either slight or no activity.

Actidione (NSC-185; SK-903) and mitomycin C (NSC-26980; SK-19256) had a strong inhibitory action on MRS No. 1, but the other ten antibiotics were inactive. Of the 16 miscellaneous compounds tested against MRS No. 1, *N*-[(3-bromopropionamido)methyl]acrylamide (NSC-66248; SK-26071) and urethane (NSC-746; SK-129) had a strong inhibitory effect, but 14 other compounds had essentially no effect.

Murphy-Sturm Rat Lymphosarcoma (MRLS)

It is evident from table 9 that MRLS is relatively resistant to alkylating agents. Among 42 compounds tested, four (10%) had a strong inhibitory effect on MRLS. DL-alanine, *N*-[3-(*p*-(bis(2-chloroethyl)amino]phenyl)-*N*-formyl-DL-alanyl]-3-phenyl-, ethyl ester (NSC-525823; SK-25823); valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-formyl-DL-alanyl]-, ethyl ester (NSC-525022; SK-25022); cyclophosphamide (NSC-26271; SK-20501); and piperazine, 1,4-dihydracryloyl-, dimethanesulfonate (NSC-47774; SK-24591) had a strong inhibitory effect on MRLS. L-Sarcolysin (NSC-8806; SK-15673), BCNU (NSC-409962; SK-27702), and 1,9-nonanediol, dimethanesulfonate (NSC-3052; SK-7505) had no inhibitory effect.

MRLS is not sensitive to pyrimidine analogs. None of the 12 compounds tested including 5-FU (NSC-19893; SK-18143) had a moderate, strong, or completely inhibitory effect on MRLS.

MRLS is not sensitive to purine analogs. Among 32 compounds tested, only *N*-hydroxy-*N*-nitrosoadenine (NSC-529509; SK-29509) had a strong inhibitory effect on MRLS. The other 31 compounds including 6-MP (NSC-755; SK-5357) had only a slight or no effect.

Among ten antimetabolites tested, aminopterin (NSC-739; SK-1072) and methotrexate (NSC-740; SK-1275) had a strong inhibitory effect on MRLS.

MRLS is not sensitive to steroids. Among 12 steroids tested, including hydrocortisone (NSC-10483E; SK-3047), none had a moderate, strong, or completely inhibitory effect on MRLS.

MRLS is not sensitive to antibiotics. Among 45 compounds tested against MRLS, two (4%) had a strong inhibitory effect. These compounds are 1*a*-benzoylmitomycin C (SK-28146) and zygosporin A (SK-30133). Actinomycin D (NSC-3053; SK-14095), mitomycin C (NSC-26980; SK-19256), and 41 other antibiotics had either slight or no activity.

All 13 quinolines tested showed no activity against MRLS and none of 81 miscellaneous compounds tested had more than a slight effect.

Rat Fibrosarcomas (RFS Nos. 1, 4, 6, and 7)

Transplantable fibrosarcoma Nos. 1, 4, 6, and 7 were induced in rats by sc administration of 3-hydroxyxanthine in 1964 (27).

1-Methyl-1-nitrosourea (NSC-23909; SK-24464) at a dose of 20 mg/kg/day had no inhibitory effect on RFS No. 1, a slightly inhibitory effect on RFS Nos. 4 and 7, and a strong inhibitory effect on RFS No. 6. BCNU (NSC-409962; SK-27702) at a dose of 8.0 mg/kg/day had a completely inhibitory effect on RFS Nos. 1, 6, and 7, but a moderately inhibitory effect on RFS No. 4. Cyclophosphamide (NSC-26271; SK–20501) at a dose of 25 mg/kg/day had a completely destructive effect on RFS Nos. 6 and

7, a strong inhibitory effect on RFS No. 1, and a moderately inhibitory effect on RFS No. 4.

5-FU (NSC-19893; SK-18143) at a dose of 25 mg/kg/day had a strong inhibitory effect on RFS Nos. 6 and 7, a moderately inhibitory effect on RFS No. 4, and no effect on RFS No. 1.

3-Hydroxyxanthine (NSC-528403; SK-28403), a strong oncogenic compound, had a strong inhibitory effect on RFS No. 4 at a dose of 35 mg/kg/day, but no effect on RFS Nos. 1, 6, and 7.

6-MP (NSC-755; SK-5357) at a dose of 30 mg/kg/day had a moderately inhibitory effect on all four rat fibrosarcomas.

The antifolic acid methotrexate (NSC-740; SK-1275) at a dose of 0.5 mg/kg/day had a strong inhibitory effect on RFS Nos. 4 and 6, a moderately inhibitory effect on RFS No. 1, but no effect on RFS No. 7.

Cortisone (NSC-49420E; SK-2795) at a dose of 37.5 mg/kg/day had a moderately inhibitory effect on RFS No. 6, a slightly inhibitory effect on RFS Nos. 4 and 7, and no effect on RFS No. 1.

Mitomycin C (NSC-26980; SK-19256) at a dose of 1.0 mg/kg/day had a strong inhibitory effect on RFS Nos. 1, 6, and 7, but a slightly inhibitory effect on RFS No. 4.

Vincristine (NSC-67574; SK-26327) at a dose of 0.125 mg/kg/day had no inhibitory effect on RFS Nos. 1 and 7. Calcium chloride (SK-3589) at a dose of 200 mg/kg/day had a moderately inhibitory effect on RFS No. 7, but no effect on RFS Nos. 1 and 6.

Babcock Rat Kidney Tumor (BRK)

Among 17 alkylating agents tested against BRK tumor, DL-alanine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-acetyl-DL-alanyl)-3-phenyl-, ethyl ester (NSC-526622; SK-26622); valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-formyl-DL-alanyl]-, ethyl ester (NSC-525022; SK-25022); 1-methyl-1-nitrosourea (NSC-23909, SK-24464); BCNU (NSC-409962; SK-27702); and cyclophosphamide (NSC-26271; SK-20501) had a moderately inhibitory effect on this tumor. Twelve other alkylating agents had either slight or no activity.

5-FU (NSC-19893; SK-18143), 6-MP (NSC-755; SK-5357), azaserine (NSC-742; SK-9505), and hydrocortisone (NSC-10483E; SK-3047) had a slightly inhibitory effect on BRK tumor.

Among 19 antibiotics tested, mitomycin C (NSC-26980; SK-19256), methyl mitomycin C (SK-20779), and porfiromycin (NSC-56410; SK-25021) had a moderately inhibitory effect on this kidney tumor. Actinomycin D (NSC-3053; SK-14095) (28) had no effect on BRK tumor. Fifteen antibiotics had either slight or no activity.

Among 26 miscellaneous compounds tested against BRK tumor, only arsenic oxide (NSC-92859; SK-29831) had a moderately inhibitory effect. All other compounds had either slight or no activity.

Novikoff Rat Hepatoma (NRH)

Among 12 alkylating agents tested against NRH, DL-valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-acetyl-DL-alanyl]-, ethyl ester (NSC-526406; SK-26406) and cyclophosphamide (NSC-26271; SK-20501) had a moderately inhibitory effect. Ten other alkylating agents had essentially no effect.

An antimetabolite, *N*-{*p*-{{[2(or 4)-amino-4(or 2)-hydroxypyrido[3,2-*d*]-pyrimidin-6-yl]methyl}amino benzoyl}-L-glutamic acid (SK-24813) had a moderately inhibitory effect.

5-FU (NSC-19893; SK-18143), 6-MP (NSC-755; SK-5357), methotrexate (NSC-740; SK-1275), cortisone (NSC-49420E; SK-2795), actinomycin D (NSC-3053; SK-14095), mitomycin C (NSC-26980; SK-19256), quinomycin A (NSC-526417; SK-26417), urethane (NSC-746; SK-129), and 21 other compounds in eight categories had essentially no effect on NRH.

Iglesias Functional Rat Ovarian Tumor (FOT)

FOT was found in a rat of A × C strain (gray coat color) in 1949 (29). It is a slow growing tumor, and 4 weeks after transplantation it reaches approximately 2.6 × 1.2 × 0.8 cm. Vascularization is abundant in this tumor. According to Iglesias (29), in a few instances a change of tumor type took place. The Iglesias rat sarcoma used in the present study is one of these transformed sarcomas; it is a sarcoma-like neoplasm that grows rapidly.

It is clear from table 16 that FOT is very sensitive to alkylating agents. Among 22 compounds tested, nine (41%) had a strong or completely inhibitory effect on FOT. BCNU (NSC-409962; SK-27702) at a dose of 8.0 mg/kg/day

and cyclophosphamide (NSC-26271; SK-20501) at a dose of 25 or 12.5 mg/kg/day had a completely inhibitory effect on FOT. Glycine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-acetyl-DL-alanyl]-, ethyl ester (NSC-526407; SK-26407); DL-valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-acetyl-DL-alanyl]-, ethyl ester (NSC-526406; SK-26406); 1-methyl-1-nitrosourea (NSC-23909; SK-24464); 1,9-nonanediol, dimethanesulfonate (NSC-3052; SK-7505); *N*-phenylsulfonyl-*P,P,P*-tris(1-aziridinyl)phosphineimide (NSC-520644; SK-20644); and phosphinic acid, bis(1-aziridinyl)-, *p*-phenylene ester (NSC-42158; SK-17360) had a strong inhibitory effect on this tumor.

2′-Deoxy-5-fluorocytidine (NSC-48006; SK-20000) had a strong inhibitory effect, but 5-FU (NSC-19893; SK-18143) had only a slightly inhibitory effect on FOT.

6-MP (NSC-755; SK-5357) and two other purines were ineffective in FOT.

Azaserine (NSC-742; SK-9505) had a moderately inhibitory effect on FOT, but methotrexate (NSC-740; SK-1275) was ineffective.

Hydrocortisone (NSC-10483E; SK-3047) and 9α-fluoro-17-hydroxy-2α-methyl corticosterone, 21-acetate (NSC-12601E; SK-18062) had a moderately inhibitory effect on FOT, but five other steroids had no effect.

FOT is sensitive to antibiotics. Among 24 antibiotics tested, 11 (46%) had a moderate, strong, or completely inhibitory effect. Mitomycin C (NSC-26980; SK-19256) at a dose of 1.0 mg/kg/day had a completely destructive effect; iyomycin B_1, hydrochloride (NSC-83340; SK-28487) at a dose of 5.0 mg/kg/day and streptonigrin (NSC-45383; SK-20556) at a dose of 0.1 mg/kg/day had a strong inhibitory effect. Actidione (NSC-185; SK-903), 1α-*p*-toluenesulfonylmitomycin C (SK-28145), 1α-chloroethylmitomycin C (SK-28242), chromomycin A_3 (NSC-58514; SK-20863), quinomycin A (NSC-526417; SK-26417), streptovitacin A (NSC-39147; SK-20250), actinobolin sulfate (NSC-31083; SK-21721), and porfiromycin (NSC-56410; SK-25021) had a moderately inhibitory effect.

Of the 20 miscellaneous compounds tested against FOT, *N,N′*-ethylenebis[3-bromo]-propionamide (NSC-49403; SK-25512) and *N,N′*-ethylenebis-, dimethanesulfonate hydracrylamide (NSC-53582; SK-25513) caused complete inhibition and strong inhibition respectively. Most of the other 18 compounds had either slight or no activity.

Iglesias Rat Sarcoma (OT)

It is clear that OT is very sensitive to alkylating agents. Among 16 compounds tested, nine (56%) had a strong inhibitory effect. These compounds are: L-sarcolysin (NSC-8806; SK-15673), the *N*-acetylsarcolysyl derivative of glycine (NSC-526407; SK-26407), the *N*-formylsarcolysyl derivative of alanine (NSC-525823; SK-25823), the *N*-acetylsarcolysyl derivative of alanine (NSC-526622; SK-26622), the *N*-formylsarcolysyl derivative of valine (NSC-525022; SK-25022), the *N*-acetylsarcolysyl derivative of valine (NSC-526406; SK-26406), the *N*-formylsarcolysyl derivative of glutamic acid (NSC-527453; SK-27453), cyclophosphamide (NSC-26271; SK-20501), and phosphinic acid, bis(1-aziridinyl)-, *p*-phenylene ester (NSC-42158; SK-17360).

Pyrimidine analogs, including 2′-deoxy-5-fluorouridine (NSC-27640; SK-19150), purine analogs, including 6-MP (NSC-755; SK-5357), antimetabolites, including azaserine (NSC-742; SK-9505), steroids, including cortisone (NSC-49420E; SK-2795), and miscellaneous compounds had essentially no effect on OT.

Of the 14 antibiotics tested against OT only mitomycin C (NSC-26980; SK-19256) had a strong inhibitory effect and other antibiotics had essentially no effect.

Iglesias Functional Rat Adrenal Tumor (AT)

AT is sensitive to alkylating agents. Among 18 compounds tested, four (22%) had a strong or completely inhibitory effect on AT. BCNU (NSC-409962; SK-27702) at a dose of 8.0 mg/kg/day caused complete destruction of the tumor. The *N*-formylsarcolysyl derivative of glycine (NSC-525691; SK-25691), the *N*-formylsarcolysyl derivative of glutamic acid (NSC-527453; SK-27453), and 5-[bis(2-chloroethyl)amino]-, DL-tryptophan (NSC-62403; SK-27456) had a strong inhibitory effect on AT. Cyclophosphamide (NSC-26271; SK-20501) and 2,4,6-tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) had only a slight inhibitory effect.

5-Bromouracil (NSC-19940; SK-1507), 6-MP

(NSC-755; SK-5357), methotrexate (NSC-740; SK-1275), and cortisone (NSC-49420E; SK-2795) had no inhibitory effect on AT.

1α-Chloroacetylmitomycin C (SK-28242) had a strong inhibitory effect on AT, while mitomycin C (NSC-26980; SK-19256), quinomycin A (NSC-526417; SK-26417), quinomycin B (NSC-526094; SK-26094), streptovitacin A (NSC-39147; SK-20250), streptonigrin (NSC-45383; SK-20556), and porfiromycin (NSC-56410; SK-25021) had a moderately inhibitory effect.

4′,4″-Di-2-imidazolin-2-yl-, terephthalanilide dihydrochloride (NSC-35843; SK-24759) at a dose of 125 mg/kg/day caused complete destruction of AT. *N,N′*-Octamethylenebis[2,2-dichloro]acetamide (NSC-59354; SK-25627) and 4′,4″-di-2-imidazolin-2-yl-2-nitro-, terephthalanilide dihydrochloride (NSC-35847; SK-24760) had a strong inhibitory effect.

There were many instances of weight loss of 10% or more in the treated animals when the MTD was administered. Although the degree of weight loss may have contributed to the antitumor effects noted (12), it was not considered to be of major importance. In general, the agents retained their antineoplastic activity when administered at doses which did not produce weight loss.

In two separate experiments (ten rats in each group), the effect of underfeeding on tumor growth was determined. Tumor-bearing rats (W256) weighing 80–100 g were fed 3 g of Purina Laboratory Chow per day. At the end of 2 weeks the tumor index (*see* table 1) in these animals was 0.61 and 0.75 respectively, an indication of slight tumor inhibition. The weight loss was 25 and 18 g, respectively. Control animals fed food ad libitum consumed approximately 11 g per day and gained 46 g during the 2-week period. The effect of underfeeding on the growth of all other tumors except FRC was not determined.

The success of cyclophosphamide and many other compounds in completely inhibiting 1-day-old tumors led to tests on well-established 7-day-old tumors.

The study showed that it was possible to cause permanent and complete regression of certain well-established 7-day-old tumors. Table 19 shows that the antitumor activity of compounds on 1-day-old and 7-day-old tumors was essentially the same, although there were instances where 1-day-old tumors responded better. The following compounds had a completely destructive action on 7-day-old tumors in 2–3 weeks: 3-pyridinol, 5-([bis(2-chloroethyl)amino]methyl)-4-(methoxymethyl)-2-methyl-, dihydrochloride, dihydrate (NSC-9506; SK-1424) on R39; L-sarcolysin (NSC-8806; SK-15673) on YRS; *N*-[3-(*p*-[bis(2-chloroethyl)amino]phenyl)-*N*-formyl-DL-alanyl]glycine, ethyl ester (NSC-525691; SK-25691) on JRS and YRS; 5-[bis(2-chloroethyl)amino]-, DL-tryptophan (NSC-62403; SK-27456) on JRS and YRS; BCNU (NSC-409962; SK-27702) on JRS and YRS; tris(1-aziridinyl)phosphine oxide (NSC-9717; SK-3818) on JRS and R39; cyclophosphamide (NSC-26271; SK-20501) on JRS; *N*-phenylsulfonyl-*P,P,P*-tris(1-aziridinyl)phosphineimide (NSC-520644; SK-20644) on JRS; 2,4,6-tris(1-aziridinyl)-*s*-triazine (NSC-9706; SK-1133) on R39; and aminopterin (NSC-739; SK-1072) on MRLS. There was no reappearance of tumors during the experimental period of 2–3 months, and on autopsy no tumor material was found at the former tumor sites. At the start of treatment these tumors had diameters of from 1.4 × 0.5 cm to 3.5 × 1.0 cm; however, 14-day-old sarcomas having diameters of approximately 6.0 × 3.0 cm were seldom completely destroyed by the agents.

DISCUSSION

The present study indicates clearly that the responses of various tumors to a given agent are strikingly different. Testing agents against a spectrum of tumors is advantageous in determining the range of activity of a given compound. It also permits the detection of the most suitable tumor for studying certain types of activity, ie, evaluation of different classes of compounds based on biologic activities. A tabulation of those compounds which gave complete inhibition of the various rat tumors is presented in table 20.

The results with various compounds tested at, or near, the MTD show that alkylating agents were most effective against FRC, W256, JRS, R39, YRS, MRS No. 1, RFS Nos. 1, 6, and 7, FOT, OT, and AT, but were not effective against MRLS, RFS No. 4, BRK, and NRH. Cyclophosphamide is one of the most effective antitumor compounds known at present. Burchenal (30) and Oettgen (31) reported that either

oral or iv administration of cyclophosphamide (NSC-26271; SK-20501) had a remarkable effect on African children with malignant lymphoma involving the jaw (Burkitt's tumor). To date, there have been more than 200 complete cures among children treated with this agent.

Pyrimidine analogs were effective against R39 and RFS No. 6, but not against 14 other tumors.

Purine analogs were effective for R39 and RFS No. 4, but were not very effective against 14 other tumors.

Antimetabolites were active against JRS, MRLS, RFS No. 1, RFS No. 4, and RFS No. 6, but did not affect 11 other tumors. It is extremely interesting to note that the folic acid antagonists, aminopterin and methotrexate, have caused temporary remission of acute leukemia in children (32, 33), as well as a number of complete cures of choriocarcinoma and chorioadenoma in women (34).

Steroids were not effective for any of the 16 tumors tested. Among 18 steroids tested none had a strong or completely inhibitory effect on these tumors.

Certain antibiotics were effective against FRC, JRS, YRS, MRS No. 1, RFS No. 1, RFS No. 6, RFS No. 7, FOT, and AT.

Thirteen quinolines were tested against six different rat tumors, FRC, W256, JRS, R39, YRS, and MRLS, but none showed a strong or completely inhibitory effect on these tumors. Certain nitroquinolines had a definite inhibitory effect on mouse tumors, both in the solid and ascites forms. The differences in response to compounds, depending on the tumor system, reemphasize the usefulness of studies on a variety of tumors.

BCNU (NSC-409962; SK-27702) was tested against four grossly and histologically identical fibrosarcomas induced in rats by 3-hydroxyxanthine (NSC-528403; SK-28403) to determine whether these four tumors responded to the agent in a similar manner. The results showed that the compound had a completely inhibitory effect on RFS Nos. 1, 6, and 7, but only a moderately inhibitory effect on RFS No. 4.

The results with cyclophosphamide (NSC-26271; SK-20501) showed that the compound had a completely inhibitory effect on RFS Nos. 6 and 7, a strong inhibitory effect on RFS No. 1, and a moderately inhibitory effect on RFS No. 4.

The results with methotrexate (NSC-740; SK-1275) showed that the compound had a completely inhibitory effect on RFS No. 6, a strong inhibitory effect on RFS No. 4, a moderately inhibitory effect on RFS No. 1, and no effect on RFS No. 7.

The results with mitomycin C (NSC-26980; SK-19256) showed that the compound had a strong inhibitory effect on RFS Nos. 1, 6, and 7, but only a slightly inhibitory effect on RFS No. 4. These diversities in effect with different compounds on similar types of tumors make it difficult to select specific agents for a given tumor.

The occurrence of cross-resistance and the development of collateral sensitivity have been observed with folic acid antagonists, alkylating agents, antimetabolites, and antibiotics by many investigators (25). Our data indicate that 15 alkylating agents, one pyrimidine, one purine, two folic acid antagonists, three antibiotics, and three miscellaneous compounds, which were effective against the mitomycin C-sensitive JRS, were relatively non-inhibitory against the mitomycin C-resistant JRS. These findings were indicative of cross-resistance but not of collateral sensitivity. Twenty-nine compounds which were inactive or slightly inhibitory against the mitomycin C-sensitive sarcoma were judged to be relatively inactive against the mitomycin C-resistant sarcoma.

In 1960, a new transplantable Babcock rat renal tumor (35) was added to the tumor spectrum because its histologic structure closely resembles Wilms' tumor in humans. It is interesting to note that actinomycin D (NSC-3053; SK-14095) was ineffective on the Babcock renal tumor and Iglesias adrenal tumor in rats despite its known effectiveness against the Wilms' tumor in children (36–38).

TABLE A.—List of compounds*

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
			I. Alkylating Agents		
750	5681	55-98-1	1,4-Butanediol, dimethanesulfonate	$O_6S_2C_6H_{14}$	6
762	101	55-86-7	Diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride (mechlorethamine; nitrogen mustard; HN_2)	$NCl_2C_5H_{11}$ · HCl	2,23
3052	7505	4248-77-5	1,9-Nonanediol, dimethanesulfonate	$O_6S_2C_{11}H_{24}$	11
3094	11687	7227-91-0	Triazene, 3,3-dimethyl-1-phenyl-	$N_3C_8H_{11}$	78–5
6396	6882	52-24-4	Phosphine sulfide, tris(1-aziridinyl)-	$N_3PSC_6H_{12}$	8,29
8806	15673	3223-07-2	Alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, monohydrochloride, L- (melphalan; L-sarcolysin)	$N_2O_2Cl_2C_{13}H_{18}$ · HCl	102
9506	1424	6304-88-7	3-Pyridinol, 5-([bis(2-chloroethyl)amino]-methyl)-4-(methoxymethyl)-2-methyl-, dihydrochloride, dihydrate	$N_2O_2Cl_2C_{13}H_{20}$ · 2HCl · 2HOH	2
9706	1133	51-18-3	*s*-Triazine, 2,4,6-tris(1-aziridinyl)-	$N_6C_9H_{12}$	8,95
9717	3818	545-55-1	Phosphine oxide, tris(1-aziridinyl)-	$N_3OPC_6H_{12}$	8,95
10107	598	302-70-5	Diethylamine, 2,2′-dichloro-*N*-methyl-, *N*-oxide, compd. with hydrochloride (1:1) (nitromin)	$NOC_5H_{11}Cl_2$ · HCl	2,53,88
14210	21739	—	Alanine, 3-[*p*-[bis(2-chloroethyl)amino]-phenyl]-, monohydrochloride, DL- (merphalan; sarcolysin)	$N_2O_2Cl_2C_{13}H_{18}$ · HCl	29
17016	6699	4672-49-5	Ethylene glycol, dimethanesulfonate	$O_6S_2C_4H_{10}$	11
21199	20656	—	Phosphonic acid, (*p*-[bis(2-iodoethyl)amino]-benzyl)-, diethyl ester	$NO_3PI_2C_{13}H_{24}$	10
23909	24464	684-93-5	Urea, 1-methyl-1-nitroso-	$N_3O_2C_2H_5$	29
26271	20501	6055-19-2	2*H*-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate (cyclophosphamide; Cytoxan)	$N_2O_2PCl_2C_7H_{15}$ · HOH	9,97
26750	12066	—	Serine, *N*-(3-chloropropionyl)-, DL-	$NO_4ClC_6H_{10}$	1
26806	22595	—	1-Aziridineethanol, α-vinyl-, mixt. with β-vinyl-1-aziridineethanol (7:3)	NOC_6H_{11}	29
34462	19849	66-75-1	Uracil, 5-[bis(2-chloroethyl)amino]-	$N_3O_2Cl_2C_8H_{11}$	10
41269	11088	13928-89-7	Piperazine, 1,4-bis(2-bromopropionyl)-	$N_2O_2Br_2C_{10}H_{16}$	17
42158	17360	1858-46-4	Phosphinic acid, bis(1-aziridinyl)-, *p*-phenylene ester	$N_4O_4P_2C_{14}H_{20}$	78–30
44593	23191	—	Theophylline, 8-[bis(2-chloroethyl)triazeno]-	$N_7O_2Cl_2C_{11}H_{15}$	2,57
46338	14913	6341-04-4	Cinnamic acid, *p*-[bis(2-chloroethyl)amino]-	$NO_2Cl_2C_{13}H_{15}$	22
47774	24591	2608-24-4	Piperazine, 1,4-dihydracryloyl, dimethanesulfonate (piposulfan)	$N_2O_8S_2C_{12}H_{22}$	17
48225	4383	2482-80-6	Pyrimidine, 2,4-bis(1-aziridinyl)-6-chloro-	$N_4ClC_8H_9$	6
48821	15128	7203-89-6	Triazene, 3,3-dimethyl-1-*p*-tolyl-	$N_3C_9H_{13}$	58
49421	4614	1907-75-1	Phosphinic amide, *P,P*-bis-(1-aziridinyl)-*N,N*-diethyl-	$N_3OPC_8H_{15}$	8
60409	26883	—	DL-alanine, *N*-(DL-2-bromopropionyl)-3-phenyl-	$NO_3BrC_{12}H_{14}$	1
62403	27456	153-88-8	Tryptophan, 5-[bis(2-chloroethyl)amino]-, DL-	$N_3O_2Cl_2C_{15}H_{19}$	78–5
64928	25813	1477-75-4	Ethylamine, 2-chloro-*N*-sulfinyl-	$NOSClC_2H_4$	60
66349	26928	3183-27-5	Propionamide, 2-acetamido-*N,N*-bis(2-chloroethyl)-	$N_2O_2Cl_2C_9H_{16}$	12
66352	26927	1462-82-4	Hydrocinnamamide, α-acetamido-*N,N*-bis(2-chloroethyl)-	$N_2O_2Cl_2C_{13}H_{20}$	12
74437	13595	2917-98-8	Piperazine, 1,4-bis(2,3-epoxypropyl)-	$N_2O_2C_{10}H_{16}$	15
84641	29102	—	1-Propanol, 3,3′-(methylimino)di-, dimethanesulfonate, hydrochloride	$NO_6S_2C_9H_{21}$ · HCl	94
136059	7503	13056-98-9	Triazene, 3,3-diethyl-1-phenyl-	$N_3C_{10}H_{15}$	78–5
408428	14405	7227-92-1	Triazene, 3,3-dimethyl-1-(*p*-nitrophenyl)-	$N_4O_2C_8H_{10}$	58
409962	27702	154-93-8	Urea, 1,3-bis(2-chloroethyl)-1-nitroso-	$N_3OCl_2C_5H_9$	29

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
520644	20644	4411-74-9	Phosphineimide, *N*-phenylsulfonyl-*P,P,P*-tris(1-aziridinyl)-	$N_4O_2PSC_{12}H_{17}$	79
520645	20645	14149-26-9	*N*-(*p*-Toluenesulfonyl)-*P,P,P*-triaziridinyl phosphineimide	$N_4O_2PSC_{13}H_{19}$	79
520646	20646	—	Phosphineimide, *N*-(*p*-methoxyphenylsulfonyl)-*P,P,P*-tris(1-aziridinyl)-	$N_4O_3PSC_{13}H_{19}$	79
520647	20647	—	Phosphineimide, *N*-(*p*-chlorophenylsulfonyl)-*P,P,P*-tris(1-aziridinyl)-	$N_4O_2PSClC_{12}H_{16}$	79
524469	24469	4700-90-7	*s*-Triazine, 2,4-bis(1-aziridinyl)-6-([bis(1-aziridinyl)methylene]amino)-	$N_8C_{12}H_{16}$	14
525022	25022	—	Valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]-phenyl)-*N*-formyl-DL-alanyl]-, ethyl ester	$N_3O_4Cl_2C_{21}H_{31}$	82,83
525691	25691	—	Glycine, *N*-[3-(*p*-[bis(2-chloroethyl) amino]-phenyl)-*N*-formyl-DL-alanyl]-, ethyl ester	$N_3O_4Cl_2C_{18}H_{25}$	82,83
525823	25823	—	DL-Alanine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]-phenyl)-*N*-formyl-DL-alanyl]-3-phenyl-, ethyl ester	$N_3O_4Cl_2C_{25}H_{31}$	82,83
526406	26406	7428-49-1	DL-Valine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]-phenyl)-*N*-acetyl-DL-alanyl]-, ethyl ester	$N_3O_4Cl_2C_{22}H_{33}$	82,83
526407	26407	—	Glycine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]-phenyl)-*N*-acetyl-DL-alanyl]-, ethyl ester	$N_3O_4Cl_2C_{19}H_{27}$	82,83
526622	26622	1620-25-3	DL-Alanine, *N*-[3-(*p*-[bis(2-chloroethyl)amino]-phenyl)-*N*-acetyl-DL-alanyl)-3-phenyl-, ethyl ester	$N_3O_4Cl_2C_{26}H_{33}$	82,83
526884	26884	—	DL-Alanine, *N*-(3-bromopropinoyl)-	$NO_3BrC_6H_{10}$	1
527408	27408	—	Purine, 6-(2-[bis(2-chloroethyl)amino]ethylthio]-, hydrochloride	$N_5SCl_2C_{11}H_{15}\cdot HCl$	78–44
527453	27453	7409-36-1	DL-Glutamic acid, *N*-[3-(*p*-[bis(2-chloroethyl)-amino]phenyl)-*N*-formyl-DL-alanyl]-, diethyl ester	$N_3O_6Cl_2C_{22}H_{33}$	82,83
528988	28988	2886-83-1	Phosphinic amide, *P,P*-bis(1-aziridinyl)-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)-	$N_5OPSC_7H_{12}$	90
529213	29213	—	Aziridine, 1,1′-[1,4-piperazinediylbis(ethylene-carbonyl)]bis-	$N_4O_2C_{14}H_{24}$	90
—	2732	—	Trimethylolmelamine	$N_6O_3C_6H_{12}$	8
—	15385	—	Phosphonitrile, bis(1-aziridinyl)-	$N_3PC_4H_8$	3
—	15749	—	Triazene, 3-cyclohexyl-3-methyl-1-*p*-tolyl-	$N_3C_{14}H_{21}$	58
—	20597	—	L-Phenylalanine, *p*-[di(2-chloroethyl)amino]-, hexyl ester	$N_2O_2Cl_2C_{19}H_{30}$	78–36,99
—	20598	—	L-Phenylalanine, *p*-[di(2-chloroethyl)amino]-, amyl ester (sarcolysin amyl ester)	$N_2O_2Cl_2C_{18}H_{28}$	78–36,99
			II. Pyrimidine Analogs		
1589	11770	—	5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-2,4-dioxo, monohydrate	$N_2O_4C_5H_4\cdot HOH$	13,78–12
3061	5051	58-14-0	Pyrimidine, 2,4-diamino-5-(*p*-chlorophenyl)-6-ethyl-	$N_4ClC_{12}H_{13}$	6
3062	5266	18588-57-3	Pyrimidine, 2,4-diamino-5-(3,4-dichlorophenyl)-6-ethyl-	$N_4Cl_2C_{12}H_{12}$	6
3277	1336	5392-28-9	Pyrimidine, 2,4,5,6-tetraamino, sulfate	$N_6C_4H_8\cdot H_2SO_4$	78–1
3425	13056	461-89-2	*as*-Triazine-3,5(2*H*,4*H*)-dione (6-azauracil)	$N_3O_2C_3H_3$	6
9791	5440	65-86-1	Orotic acid	$N_2O_4C_5H_4$	1,2
19893	18143	51-21-8	Uracil, 5-fluoro-	$N_2O_2FC_4H_3$	5
19940	1507	51-20-7	Uracil, 5-bromo-	$N_2O_2BrC_4H_3$	6
20258	3816	65-46-3	Cytidine	$N_3O_5C_9H_{13}$	
27640	19150	—	Uridine, 2′-deoxy-5-fluoro-	$N_2O_5FC_9H_{11}$	5
31712	18354	—	Orotic acid, 5-fluoro-, monohydrate	$N_2O_4FC_5H_3\cdot HOH$	5

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
48006	20000	—	Cytidine, 2′-deoxy-5-fluoro-	$N_3O_4FC_9H_{12}$	5,78–12
67670	20298	—	Uridine, 2′-deoxy-5-fluoro-, 3′,5′-diacetate	$N_2O_7FC_{13}H_{15}$	5
73376	6959	13115-81-6	Isobarbituric acid, 1-β-D-ribofuranosyl- (5-hydroxyuridine)	$N_2O_7C_9H_{12}$	61
146604	19273	316-46-1	Uridine, 5-fluoro-	$N_2O_6FC_9H_{11}$	5
514427	14427	2443-50-7	*N*-(2′-Methyl-4′-aminopyrimidyl-5′) methyl-4-methyl-5-β-hydroxyethyl thiothiazolone (2) hydrochloride	$N_4OS_2C_{12}H_{16}\cdot HCl$	65,78–22
520866	20866	2877-65-8	Benzenesulfonic acid, 4-(2,4,6-triamino-5-pyrimidinylazo)-	$N_7O_3SC_{10}H_{11}$	81
529351	29423	—	Uracil, 5-(mercaptomethyl)-	$N_2O_2SC_5H_6$	78–23
—	6883	—	2,4,6-Tris(2-vinylaziridino-2-triazine	$N_6C_{15}H_{15}$	8
—	29217	—	1-(6-Amino-4-pyrimidinyl)-2-(5-nitro-2-furyl) ethylene	$N_4O_3C_{10}H_8$	91
—	29511	—	Pyrimidine, 4-[5-nitro-2-furylvinyl]-	$N_3O_3C_{10}H_7$	91
			III. Purines and Analogs		
743	1395	—	Purine, 2,6-diamino-, monohydrate	$N_6C_5H_6\cdot HOH$	6
744	6048	87-42-3	Purine, 6-chloro-	$N_4ClC_5H_3$	78–5
749	1150	529-99-7	7*H*-*v*-Triazolo[4,5-*d*]pyrimidin-7-one, 5-amino-1, 6-dihydro-(8-azaguanine)	$N_6OC_4H_4$	8,29,78–1
752	5459	1832-72-0	Purine-6-thiol, 2-amino- (6-thioguanine)	$N_5SC_5H_5$	6
753	8709	120-73-0	Purine hydrochloride	$N_4C_5H_4\cdot HCl$	29,78–3
755	5357	6112-76-1	Purine-6-thiol, monohydrate (6-mercaptopurine)	$N_4SC_5H_4\cdot HOH$	6,29,35
756	1149	552-69-2	*v*-Triazolo[4,5-*d*]pyrimidine-5,7-diol (8-azaxanthine)	$N_5O_2C_4H_3$	6,8,78–1
759	1509	51-17-2	Benzimidazole	$N_2C_7H_6$	6,11
3057	1054	—	*v*-Triazolo[4,5-*d*]pyrimidine, 5,7-diamino-, sulfate (1:1)	$N_7C_4H_5\cdot H_2SO_4$	6,78–1
3702	1493	5324-53-8	Guanine	$N_5OC_5H_5$	3,34
4911	12355	574-25-4	9*H*-Purine-6-thiol, 9-β-D-ribofuranosyl	$N_4O_4SC_{10}H_{12}$	28,29
14664	1494	69-89-6	Xanthine	$N_4O_2C_5H_4$	34
14666	1387	73-24-5	Adenine	$N_5C_5H_5$	2,34
17109	3338	5446-89-9	Hypoxanthine, 2-(methylthio)-	$N_4OSC_6H_6$	6
25165	18094	—	1*H*-Imidazo[4,5-*d*]pyridazine, 4-amino-, monohydrochloride	$N_5C_5H_5\cdot HCl$	17
25650	14944	6165-02-2	Purine, 6-(2,2-dimethylhydrazino)-	$N_6C_7H_{10}$	1
25652	17902	—	Pyrazolo[3,4-d]pyrimidine, 4-[(*o*-methylbenzyl) amino]-	$N_5C_{13}H_{13}$	1,57
29422	18615	85-31-4	9*H*-Purine-6-thiol, 2-amino-9-β-D-ribofuranosyl-(6-mercaptopurine riboside)	$N_5O_4SC_{10}H_{13}$	2
38887	20355	5581-52-2	Purine, 2-amino-6-[(1-methyl-4-nitroimidazol-5-yl) thio]- (thiamiprine)	$N_7O_2SC_9H_7$	6
39084	20354	—	Purine, 6-[(1-methyl-4-nitroimidazol-5-yl) thio]-, monohydrate (azathioprine)	$N_7O_2SC_9H_7\cdot HOH$	6
39336	25531	24397-95-3	9*H*-Purine-6-thiol, 2-amino-9-butyl-	$N_5SC_9H_{13}$	29
43405	13470	16714-57-1	Purine-6(1*H*)-thione, 2-amino-1-methyl-	$N_5SC_6H_7$	6,29
45153	25533	—	9*H*-Purine-6-thiol, 9-(tetrahydro-2-furyl)-	$N_4OSC_9H_{10}$	29
48716	25532	1513-63-9	Purine-6-sulfonyl fluoride	$N_4O_2SC_5H_3F$	29
56408	26996	69-33-0	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-amino-7-β-D-ribofuranosyl-	$N_4O_4C_{11}H_{14}$	10,29
58385	14377	19447-73-5	Thiocyanic acid, purin-6-yl ester	$N_5SC_6H_3$	6
77640	7347	—	Purine, 6,6′-dithiodi-, hydrate	$N_8S_2C_{10}H_6\cdot HOH$	6
110037	17359	—	Adenine, 1-oxide, monohydrate	$N_5OC_5H_5\cdot HOH$	78–24
513473	13473	—	Purine, 6-(glucopyranosylthio)-	$N_4O_5SC_{11}H_{14}$	6
520950	20950	13265-04-8	Disulfide, bis(9-β-D-ribofuranosyl-6-purinyl)-	$N_8O_8S_2C_{20}H_{22}$	78–12
526180	26180	2568-37-8	Purine, 6-(trichloromethyl)-	$N_4Cl_3C_6H_3$	78–3,78–46

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
526485	26485	15139-51-2	Pseudourea, 2-purin-6-yl-2-thio-, hydrochloride	$N_6SC_6H_6 \cdot HCl$	78–4
527612	27612	—	Guanine, oxide	$N_5O_2C_5H_5$	78–4
528013	28013	145-95-9	Purine-6-thiol-, 3-oxide (6-mercaptopurine 3-oxide)	$N_4OSC_5H_4$	78–4
528403	28403	—	Xanthine, 7(or 9)- (3-hydroxyxanthine)	$N_4O_2C_5N_4$	78–4
528837	28837	—	Purine-6-methanethiol, 7(or 9)-acetyl-	$N_4OSC_7H_8$	78–23
529509	29509	25732-27-8	Adenine, *N*-hydroxy-*N*-nitroso-	$N_6O_2C_5H_4$	78–23
—	4901	—	5-Methyl-2-1-arabobenzimidazole	$N_2O_4C_{12}H_{16}$	2
—	19994	—	*s*-Triazolo(4,3-*a*)pyrimidine	$N_4C_5H_4$	78–30
—	29830	—	Xanthine-3-oxide, copper chelate	$N_4O_2CuC_5H_4$	78–4
—	30002	—	2,6-Dihydroxylaminopurine	$N_6O_2C_5H_6$	78–23
			IV. Antimetabolites and Folic Acids		
739	1072	—	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl) methyl]amino]benzoyl]- (aminopterin)	$N_8O_5C_{19}H_{20}$	8
740	1275	—	Glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]- (methotrexate)	$N_8O_5C_{20}H_{22}$	8
742	9505	115-02-6	Serine, diazoacetate (ester), L- (azaserine)	$N_2O_4C_5H_7$	1,62
1393	13148	2380-63-4	1*H*-Pyrazolo[3,4-*d*]pyrimidine, 4-amino-	$N_5C_5H_5$	57
3063	591	148-51-6	3-Pyridinemethanol, 5-hydroxy-4,6-dimethyl-, hydrochloride	$NO_2C_8H_{11} \cdot HCl$	2
3073	642	—	Glutamic acid, *N*-[*p*-([(2-amino-4-hydroxy-6-pteridinyl)methyl]amino)benzoyl]- (folic acid)	$N_7O_6C_{19}H_{19}$	8
5197	13640	—	1*H*-Pyrazolo[3,4-*d*]pyrimidine, 4-(methylamino)-, dihydrate	$N_5C_6H_7 \cdot 2HOH$	57
7365	13835	—	Norleucine, 6-diazo-5-oxo-, L-	$N_2O_2C_6H_9$	36
107136	1414	—	L-(+)-Aspartic acid, *N*-[*p*-[[(2-amino-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-	$N_7O_6C_{18}H_{17}$	8
—	860	—	Glutamic acid, pteroyl glutamyl glutamyl (teropterin)	$N_8O_{12}C_{29}H_{33}$	8
—	1332	—	4-Amino pteroylaspartic acid *dl* (amino-an-fol)	$N_8O_5C_{18}H_{19}$	8
—	1418	—	2-Thiophenealanine	$NO_2C_7H_9$	68,69
—	1718	—	Glutamic acid, pteroyl di- (diopterin)	$N_8O_6C_{24}H_{26}$	8
—	1833	—	2,4-Diamino-7-hydroxypteridine-6-carboxylic acid	$N_6O_3C_7H_6$	6
—	15894	—	Pyridoxine, 4-deoxy-, phosphoric acid	$NO_5C_8H_{11} \cdot H_3PO_4$	2
—	24813	—	*N*-{*p*-{{[2(or 4)-Amino-4(or 2)-hydroxypyrido[3,2-*d*]pyrimidin-6-yl]methyl}amino}benzoyl}-L-glutamic acid	$N_8O_6C_{20}H_{20}$	1
—	24815	—	Glutamic acid, *N*-{*p*-{[(2-amino-4-hydroxy-6-quinazolinyl)methyl]amino}benzoyl}-L-	$N_5O_6C_{21}H_{21}$	1
—	28757	—	*N*-[*p*[[(2-Amino-4-hydroxy-6-quinazolinyl)methyl]amino]benzoyl]-L-aspartic acid, monohydrate	$N_5O_6C_{20}H_{19} \cdot H_2O$	1
			V. Steroids		
3351E	17469	434-22-0	Estr-4-en-3-one, 17β-hydroxy- (19-nortestosterone)	$O_2C_{18}H_{26}$	10,29
9166E	2799	57-85-2	Testosterone, propionate	$O_3C_{22}H_{32}$	19,63
9564E	17653	68-22-4	Estr-4-en-3-one, 17α-ethynyl-17-hydroxy-19-Nor-17α-pregn-4-en-20-yn-3-one, 17-hydroxy-19-Nortestosterone, 17-ethynyl-	$O_2C_{20}H_{26}$	29
9565E	2931	434-03-7	Androst-4-en-3-one, 17α-ethynyl-17-hydroxy-17α-Pregn-4-en-20-yn-3-one, 17-hydroxy-Testosterone, 17-ethynyl-	$O_2C_{21}H_{28}$	19
10483E	3047	50-23-7	Cortisol (hydrocortisone)	$O_5C_{21}H_{30}$	2
10704E	16816	76-43-7	Androst-4-en-3-one, 9-fluoro-11β, 17β-dihydroxy-17-methyl-	$O_3FC_{20}H_{29}$	10,29

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
12198E	21102	—	5α-Androstan-3-one, 17β-hydroxy-2α-methyl-, propionate (dromostanolone propionate)	$O_3C_{23}H_{36}$	29
12600E	15347	338-98-7	Pregna-1,4-diene-3,20-dione, 9-fluoro-11β,17,21-trihydroxy-, 21-acetate Prednisolone, 9-fluoro-, 21-acetate	$O_6FC_{23}H_{29}$	3,29
12601E	18062	1524-87-4	Pregn-4-ene-3,20-dione, 9-fluoro-11β,17,21-trihydroxy-2α-methyl-, 21-acetate	$O_6FC_{24}H_{33}$	29
15468E	3144	68-96-2	Pregn-4-ene-3,20-dione, 17-hydroxy- Progesterone, 17-hydroxy-	$O_3C_{21}H_{30}$	10,63
17592	24924	630-56-8	Pregn-4-ene-3,20-dione, 17-hydroxy-, hexanoate Progesterone, 17-hydroxy-, hexanoate	$O_4C_{27}H_{40}$	3
20293E	10696	57-91-0	Estra-1,3,5(10)-triene-3,17α-diol (17α-estradiol)	$O_2C_{18}H_{24}$	7,11
23759E	20379	968-93-4	1-Phenanthrenepropionic acid, 1,2,3,4,4a, 4b, 7, 9,10,10a-decahydro-2-hydroxy-2,4b-dimethyl-7-oxo-, δ-lactone (testolactone)	$O_3C_{19}H_{24}$	3,29
49420E	2795	50-04-4	Cortisone, 21-acetate Pregn-4-ene-3,11,20-trione, 17,21-dihydroxy-, 21-acetate (cortisone)	$O_6C_{23}H_{30}$	2
50908E	27754	53-42-9	5β-Androstan-17-one, 3α-hydroxy-	$O_2C_{19}H_{30}$	78–8
—	2932	—	21-Acetoxy-17α-hydroxy-Δ⁴-pregnene-3,20-dione	$O_5C_{23}H_{32}$	37
—	3058	—	Δ⁴-Pregnen-17α,20β,21-triol-3-one, 20β,21-diacetate	$O_6C_{25}H_{34}$	10,37
—	3092	—	3-β-Acetoxy-Δ^{5,16}-pregnadien-20-one	$O_3C_{23}H_{32}$	19
			VI. Antibiotics		
185	903	7006-21-5	Glutarimide, 3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]- (cycloheximide; actidione)	$NO_4C_{15}H_{23}$	10
186	531	1086-03-9	3*H*-2-Benzopyran-7-carboxylic acid, 4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-	$O_5C_{13}H_{14}$	2
3053	14095	—	Actinomycin D (dactinomycin)	$N_{12}O_{16}C_{62}H_{86}$	54
3055	12414	—	Adenosine, 3′-(α-amino-*p*-methoxyhydrocinnamamido)-3′-deoxy-*N*,*N*-dimethyl-, dihydrochloride (puromycin, dihydrochloride)	$N_7O_5C_{22}H_{29}\cdot 2HCl$	8
3067	2662	—	*N*, 4′-Bi[pyrrole-2-carboxyamide], *N*′-(2-carbamoyl-ethyl)-4-[(2-guanidinoacetimidoyl) amino]-1,1′-dimethyl-, tetrahydrochloride (netropsin)	$N_{10}O_2C_{16}H_{22}\cdot 4HCl$	7
3069	2155	—	Acetamide, 2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-nitrophenethyl]-(chloramphenicol)	$N_2O_5Cl_2C_{11}H_{12}$	1,64
9168	6258	23110-15-8	2,4,6,8-Decatetraenedioic acid, 4-(1,2-epoxy-1,5-dimethyl-4-hexenyl)-5-methoxy-1-oxaspiro [2,5])oct-6-yl ester (fumagillin)	$O_7C_{26}H_{34}$	10,17
9169	2859	2058-46-0	2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-, monohydrochloride (oxytetracycline, hydrochloride) (terramycin, hydrochloride)	$N_2O_9C_{22}H_{24}\cdot HCl$	7
13252	1333	—	2-Naphthacenecarboxamide, 7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a pentahydroxy-6-methyl-1,11-dioxo-, monohydrochloride (chlorotetracycline)	$N_2O_8ClC_{22}H_{23}\cdot HCl$	8
14083	4516	—	Streptomycin, sulfate (3:2)	$N_7O_{12}C_{21}H_{39}\cdot 2/3\ H_2SO$	3
14347	12772	874-21-5	Cyclopentanecarboxylic acid, 2-methylene-3-oxo-, sodium salt (sarkomycin)	$O_3C_7H_8\cdot Na$ salt	86

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
17257	17442	—	Glutarimide, 3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-, benzoylacetate (actidione, benzoylacetate)	$NO_6C_{24}H_{29}$	10
18268	11822	—	Actinomycin C Actinomycin A and S	$N_{12}O_{16}C_{64}H_{90}$	5,38
24559	20047	18378-89-7	Mithramycin	$O_{24}C_{52}H_{76}$	7
25792	12878	—	Actinomycin B	Unknown	2,7,54
26980	19256	50-07-7	Azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indol-4,7-dione, 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-5-methyl-, carbamate (ester) (mitomycin C)	$N_4O_5C_{15}H_{18}$	2,20,29,80
31083	21721	24397-89-5	Isocoumarin, 4-(2-aminopropionamido)-3,4,4*a*,5,6,7-hexahydro-5,6,8-trihydroxy-3-methyl-(actinobolin sulfate)	$N_2O_6C_{13}H_{20}$	62
34533	19804	126-07-8	Spiro[benzofuran-2(3*H*),1′-[2]cyclohexene]-3,4′-dione, 7-chloro-2′,4,6-trimethoxy-6′-*β*-methyl- (griseofulvin)	$O_6ClC_{17}H_{17}$	2
39147	20250	523-86-4	Glutarimide, 3-[2-hydroxy-2-(5-hydroxy-3,5-dimethyl-2-oxocyclohexyl)ethyl]- (streptovitacin A)	$NO_5C_{15}H_{23}$	10
45383	20556	632-62-2	Picolinic acid, 5-amino-6-(7-amino-5,8-dihydro-6-methoxy-5,8-dioxo-2-quinolyl)-4-(2-hydroxy-3,4-dimethoxy-phenyl)-3-methyl- (streptonigrin)	$N_4O_5C_{23}H_{22}$	7
48077	20403	—	Actinomycin P_2	$N_{12}O_{19}C_{62}H_{90}$	7
51812	24907	6625-20-3	2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,10,12,12*a*-tetrahydroxy-1,11-dioxo-, monohydrochloride (sancycline)	$N_2O_7C_{23}H_{22}\cdot HCl$	7
52947	27773	—	Pactamycin	$N_4O_6C_{29}H_{39}$	29
53104	21568	1874-54-0	Adenine, 9-*β*(or *α*)-D-psicofuranosyl)	$N_5O_5C_{15}H_{19}$	10
56408	26996	69-33-0	7*H*-Pyrrolo[2,3-*d*]pyrimidine, 4-amino-7-*β*-D-ribofuranosyl- (tubercidin)	$N_4O_4C_{11}H_{14}$	10,29
56410	25021	801-52-5	Carbonic acid, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydroxymethyl)-8*a*-methoxy-1,5-dimethylazirino-[2′,3′:3,4]pyrrolo[1,2-a]-indol-4,7-dione (porfiromycin)	$N_4O_5C_{16}H_{20}$	1,10
58368	13617	30418-36-1	2,4,6,8-Decatetraenedioic acid, 4-(1,2-epoxy-1,5-dimethyl-4-hexenyl)-5-methoxy-1-oxaspiro[2,5]oct-6-yl ester, compd. with dicyclohexylamine (1:1) Fumagillin, compd. with dicyclohexylamine (1:1)	$O_7C_{26}H_{34}\cdot NC_{12}H_{23}$	17
58514	20863	7059-24-7	Chromomycin A_3	$O_{28}C_{57}H_{82}$	81
58856	25707	—	Ayamycin A_2	$O_{10}C_{28}H_{35}$	89
59729	28430	—	Sparsomycin	$N_3O_6S_2C_{13}H_{21}$	10,29
64393	14155	—	Spiramycin, hydrochloride	$N_2O_{14}C_{43}H_{74}\cdot HCl$	2,39
65423	9749	—	9*H*-Purine, 9-*β*-D-ribofuranosyl- (nebularin)	$N_4O_4C_{10}H_{12}$	78–4
76029	13328	—	3-Isoxazolidone, 4-amino- (cycloserine)	$N_2O_2C_3H_6$	55
83340	28487	—	Iyomycin B_1, hydrochloride	Unknown	92
105388	17277	—	Lagosin	$O_{14}C_{21}H_{66-70}$	84
400978	4996	1146-04-9	Illudin M Spiro[cyclopropane-1,5′-[5*H*]inden]-7′ (6′*H*)-one, 2′3′-dihydro-3′,6′-dihydroxy-2′,2′,4′,6′-tetramethyl-	$O_3C_{15}H_2O$	33
402815+	2405	7477-78-3	4-Thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, potassium salt (penicillin G)	$N_2O_4SC_{16}H_{19}\cdot K$ salt	2

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
521007	21007	—	Adenine, 9-(β-D-glucofuranosyloxy)-, 2′ (or 3′)-sulfamate (ester) (nucleocidin)	$N_6O_6SC_{11}H_{14}$	8
521778	21778	2618-22-6	Glysine, *N*-formyl-*N*-hydroxy-, sodium salt (hadacidin)	$NO_4C_3H_4 \cdot Na$ salt	2
524678	24678	—	Mitomycin D	—	80
525822	25822	—	Quinomycin C (from Streptomyces H-732)	—	89
526094	26094	—	Quinomycin B	Unknown	89
526368	26368	—	Triostin complex	Unknown	89
526417	26417	512-64-1	Echinomycin (quinomycin A)	$N_7O_7SC_{29}H_{29}$	89
526598	26598	—	Aureolic acid, magnesium deriv.	$O_{20-21}C_{30-60}$	17
—	862	—	Actinomycin	—	2
—	1732	—	Aerosporin (polymyxin B) HCl	Unknown	7
—	2163	—	Gramicidine	—	25
—	2935	—	Cyclopentanecarboxylic acid, 2-(7-cyano-8,16-dihydroxy-9,11,13,15-tetramethyl-18-oxooxacyclooctadeca-4,6-dien-2-yl)-, sodium salt (borrelidin)	$NO_6C_{28}H_{42} \cdot Na$	5
—	12501	—	Acetylhydro-actinomycin	—	2
—	12780	—	Actinomycinol	Unknown	2
—	16701	—	Actinomycin J	$N_{12}O_{17}C_{62}H_{88}$	96
—	18355	—	Alazopeptin	$C_{13}H_{21}N_7O_6$	55
—	19439	—	Kanamycin sulfate (crystalline)	$N_4O_{11}C_{18}H_{36} \cdot H_2SO_4$	20
—	20779	—	Methyl mitomycin C		2
—	28008	—	1α-Acetylmitomycin C	$N_4O_6C_{17}H_{20}$	80
—	28009	—	1α-Propionylmitomycin C	$N_4O_6C_{18}H_{22}$	80
—	28010	—	1α-Butroylmitomycin C	$N_4O_6C_{19}H_{24}$	80
—	28145	—	1α-*p*-Toluenesulfonylmitomycin C	$N_4O_7SC_{22}H_{24}$	80
—	28146	—	1α-Benzoylmitomycin C	$N_4O_6C_{22}H_{22}$	80
—	28242	—	1α-Chloroacetylmitomycin C	$N_4O_6ClC_{17}H_{19}$	80
—	30133	—	Zygosporin A	Unknown	89
			VII. Quinolines		
346	9408	607-35-2	Quinoline, 8-nitro-	$N_2O_2C_9H_6$	41
782	14136	1477-60-7	Cinchoninaldehyde, thiosemicarbazone	$N_4SC_{11}H_{10}$	41
3396	2397	91-22-5	Quinoline	NC_9H_7	41
4141	11874	613-50-3	Quinoline, 6-nitro-	$N_2O_2C_9H_6$	41
19645	16292	—	Quinoline, 4-nitro-, 1-oxide	$N_2O_3C_9H_6$	87
21655	13198	—	Quinoline, 1-oxide, hydrochloride	$NOC_9H_7 \cdot HCl$	41
528995	28995	735-84-2	Quinoline, 2-[2-(5-nitro-2-furyl) vinyl]-	$N_2O_3C_{15}H_{10}$	93
528996	28996	858-15-1	Lactic acid, compd. with 2-amino-4-[2-(5-nitro-2-furyl) vinyl]-quinoline (1:1)	$N_2O_3C_{15}H_{11} \cdot C_3H_6O_3$	93
528997	28997	3112-60-5	4-Quinolinecarboxylic acid, 2-[2-(5-nitro-2-furyl) vinyl]-, sodium salt	$N_2O_5C_{16}H_{10} \cdot Na$ salt	93
529103	29103	908-36-1	Lactic acid, compd. with 4-amino-2-[2-(5-nitro-2-furyl) vinyl] quinoline (1:1)	$N_2O_3C_{15}H_{11} \cdot C_3H_6O_3$	93
529104	29104	—	Quinoline, 2-[2-(5-nitro-2-furyl) vinyl]-, 1-oxide	$N_2O_4C_{15}H_{10}$	93
529105	29105	798-64-1	Cinchoninamide, 2-[2-(5-nitro-2-furyl) vinyl]-	$N_3O_4C_{16}H_{11}$	93
—	16293	—	Quinoline, 2-ethyl-4-nitro-, 1-oxide	$N_2O_3C_{11}H_{10}$	87
			VIII. Miscellaneous Compounds		
4	3844	121-66-4	Thiazole, 2-amino-5-nitro-	$N_3O_2SC_3H_3$	4
139	27091	59-89-2	Morpholine, 4-nitroso-	$N_2O_2C_4H_8$	16
405	23102	50-97-5	2-Benzimidazolemethanol, α-phenyl-	$N_2OC_{14}H_{12}$	2
746	129	51-79-6	Ethyl carbamate (urethane)	$NO_2C_3H_7$	3,15
747	6479	79-16-3	Acetamide, *N*-methyl-	NOC_3H_7	21,49
748	7078	75-12-7	Formamide	$NOCH_3$	11
751	5393	67-21-0	Butyric acid, 2-amino-4-(ethylthio)-, DL-	$NO_2SC_6H_{13}$	48

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
757	280	7006-15-7	Benzo[α]heptalene-9(5*H*)-one, 7-acetamido-6, 7-dihydro-1,2,3,10-tetramethoxy- (colchicine)	$NO_6C_{22}H_{25}$	15
758	1812	66-84-2	D-Glucose, 2-amino-2-deoxy-, hydrochloride	$NO_5C_6H_{13}\cdot HCl$	11
2100	384	59-87-0	2-Furaldehyde, 5-nitro-, semicarbazone (nitrofurazone)	$N_4O_4C_6H_6$	67
2190	382	111-71-7	Heptanal (*n*-heptaldehyde)	OC_7H_{14}	11,13
3051	8328	123-39-7	Formamide, *N*-methyl-	NOC_2H_5	30
3054	3501	598-55-0	Carbamic acid, methyl ester	NOC_2H_5	13
3060	420	13464-35-2	Potassium arsenite	$KAsO_2$	—
3065	10826	3180-56-1	Isoalloxazine, 10-(2-hydroxyethyl)-7,8-dimethyl-	$N_4O_3C_{14}H_{14}$	10
3070	2800	—	4,4′-Stilbenediol, α,α'-diethyl-diethylstilbestrol	$O_2C_{18}H_{20}$	2,30
3071	12356	614-13-1	*p*-Benzoquinone, 2-methoxy-5-methyl-	$O_3C_7H_6$	2
3089	14950	61-73-4	Methylene blue	$N_3SClC_{16}H_{18}$	—
3095	2917	4375-11-5	Imidodicarboxylic acid, dihydrazide	$N_5O_2C_2H_7$	8,28
3096	11626	—	Colchicine, *N*-deacetyl-*N*-methyl- (demecolcine)	$NO_5C_{21}H_{25}$	43
3769	610	109-77-3	Malononitrile	$N_2C_3H_2$	78–3
4463	6938	—	Benzenesulfonamide, *p*-(3,3-diethyl-1-triazeno)-	$N_4O_2SC_{10}H_{14}$	13
4645	5959	1072-71-5	1,3,4-Thiadiazole, 2,5-dithiol-	$N_2S_3C_2H_2$	50
4730	14406	13275-68-8	1,3,4-Thiadiazole, 2-(ethylamino)-	$N_3SC_4H_7$	76
4794	1356	54-64-8	Mercury, [(*o*-carboxyphenyl)-thio]ethyl-, sodium salt	$O_2SH_9C_9H_{10}\cdot Na$ salt	15
5354	1147	95-54-5	*o*-Phenylenediamine	$N_2C_6H_8$	78–4
6170	50	5392-40-5	2,6-Octadienal, 3,7-dimethyl- (citral; geranialdehyde)	$OC_{10}H_{16}$	102
6289	3687	111-48-8	Ethanol, 2,2′-thiodi-	$O_2SC_4H_{10}$	3
7785	8803	79-06-1	Acrylamide	NOC_3H_5	8
7786	13943	—	Glutamic acid, 5-hydrazide, L-	$N_3O_3C_5H_{11}$	36,98
8102	8028	10257-28-0	*d*-Galactose	$O_6C_6H_{12}$	—
8538	19801	5402-71-1	Phenol, 2,2′,2″-*s*-trithiane-2,4,6-triyltri-	$O_3S_3C_{21}H_{18}$	2
9170	15025	2731-16-9	Colchicine, *N*-deacetylthio-	$NO_4SC_{20}H_{23}$	42
9242	25515	123-46-6	Trimethyl acethydrazide ammonium chloride	$N_3OClC_5H_{14}$	104
9369	20035	70-25-7	Guanidine, 1-methyl-3-nitro-1-nitroso-	$N_4O_3C_2H_5$	29
10924	156	—	2-Cyclopenten-1-one, 5-cinnanylidene-4-hydroxy-3,4-diphenyl-	$O_2C_{26}H_{20}$	1
11926	26153	313-67-7	Aristolochic acid	$NO_7C_{17}H_{11}$	7
12693	23315	2490-89-3	Urea, (*p*-arsenosophenyl)-	$N_2O_2AsC_7H_7$	79
12865	11258	6119-46-6	Quinine, hydrobromide, hydrate	$N_2O_2C_{20}H_{24}\cdot HBr\cdot HOH$	2
13875	1905	645-05-6	Hexamethylmelamine	$N_6C_9H_{18}$	1,8
14574	1471	548-57-2	Thioxanthen-9-one, 1-[[2-diethylamino)ethyl]amino]-4-methyl-, monohydrochloride (miracil D)	$N_2OSC_{20}H_{24}\cdot HCl$	6,30
15193	7305	—	D-Glucose, 2-deoxy-	$O_5C_6H_{12}$	—
17559	22575	—	Galactonitrile, pentaacetate	$NO_{10}C_{16}H_{21}$	29
21206	15928	329-89-5	Nicotinamide, 6-amino-	$N_2OC_6H_7$	2,3,77
21666	25825	—	Phenazine, 5,10-dioxide	$N_2O_2C_{12}H_8$	59
23306	26081	—	Hydantoin, 1,3-dichloro-5,5-bis(*p*-chlorophenyl)-	$N_2O_2Cl_4C_{15}H_8$	56
24854	20895	—	DL-Serine, *N*-dichloroacetyl-	$NO_4Cl_2C_5H_7$	1
25647	2401	5836-39-5	Benzenesulfonamide, *p*-(3,5-dimethyl-4-nitroso-1-pyrazolyl)-	$N_4O_3SC_{11}H_{12}$	1
25648	5326	—	4,4′-Bi-*o*-cresol, 6,6′-diallyl-α,α'-bis(methylamino)-	$N_2O_2C_{22}H_{28}$	1
25649	8856	20401-90-5	Indole-3-propionic acid, hydrazide	$N_3OC_{11}H_{13}$	1
27223	16767	50-78-2	Acetylsalicylic acid	$O_4C_9H_8$	—
30418	16850	57-53-4	Carbamic acid, 2-methyl-2-propyltrimethylene ester	$N_2O_4C_9H_{18}$	27

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
31659	19453	4348-92-9	Glutarimide, 3-[2-hydroxy-2(5-hydroxy-3,5-dimethyl-2-oxocyclohexyl) ethyl]-, diacetate	$NO_7C_{19}H_{27}$	7
32065	22591	127-07-1	Hydroxyurea	$N_2O_2CH_4$	29
33963	18766	—	Butyric acid, α-hydrazino-ω-cyclohexyl	$N_2O_2C_{10}H_{20}$	17
34162	16844	366-60-9	Pyridinium, 2-bromo-1-(*p*-fluorophenacyl) bromide	$NOBrFC_{13}H_{10} \cdot Br$	55
34540	24297	1758-73-2	Methanesulfinic acid, aminoimino-	$N_2O_2SCH_4$	7
35843	24759	2545-16-6	Terephthalanilide, 4'4''-di-2-imidazolin-2-yl-, dihydrochloride	$N_6O_2C_{22}H_{24} \cdot 2HCl$	103
35847	24760	5318-78-5	Terephthalanilide, 4'4''-di-2-imidazolin-2-yl-2-nitro-, dihydrochloride	$N_7O_4C_{22}H_{23} \cdot 2HCl$	29
36390	436	—	Podophyllum	Unknown	2
36539	24298	931-08-8	Pyrazole-1-carboxamide	$N_3OC_4H_5$	7
37538	21569	1187-00-4	Mannitol, 1,6-dimethanesulfonate, D-	$O_{10}S_2C_8H_{18}$	102
38280	24761	1820-92-4	Terephthalanilide, 2-chloro-4',4''-di'-2-imidazolin-2-yl-, dihydrochloride	$N_6O_2ClC_{22}H_{23} \cdot 2HCl$	29
38583	1417	148-18-5	Carbamic acid, diethyldithio-, sodium salt	$NS_2C_5H_{11} \cdot Na$ salt	—
44690	1039	2150-48-3	Iron, tetrachlorobis[(6-diethylamino)-3*H*-xanthen-3-ylidene]- diethylammonium]titetrachloride (purified pyronine B)	$N_2OC_{21}H_{27} + HCl$ $Fe(III)Cl_3N_7O$	32
45409	24299	1794-34-9	Pyrazole-1-carboxamide, thio-	$N_3SC_4H_5$	7
46096	3615	556-52-5	Glycidol	$O_2C_3H_6$	8
49403	25512	—	Propionamide, *N,N'*-ethylenebis[3-bromo]-	$N_2O_2Br_2C_8H_{14}$	17
53582	25513	—	Hydracrylamide, *N,N'*-ethylenebis-, dimethanesulfonate	$N_2O_8S_2C_{10}H_{20}$	17
54186	24580	—	Serine, dichloroacetate, (ester), hydrochloride, DL-	$NO_4Cl_3C_5H_7 \cdot HCl$	12
59354	25627	1477-57-2	Acetamide, *N,N'*-octamethylenebis[2,2-dichloro]-	$N_2O_2Cl_4C_{12}H_{20}$	30
64074	9113	1094-08-2	Phenothiazine, 1-10-[2-(diethylamino) propyl]-, hydrochloride	$N_2SC_{20}H_{24} \cdot HCl$	31
64075	9112	—	Phenothiazine, *d*-10-[2-(diethylamino) propyl]-, *d*-tartrate (1:1)	$N_2SC_{20}H_{24} \cdot O_4C_4H_6$	31
65448	759	142-68-7	Tetrahydropyran	OC_5H_{10}	1
66248	26071	4213-51-8	Acrylamide, *N*-[(3-bromopropionamido) methyl]-(hydracrylamide)	$N_2O_2BrC_7H_{11}$	76
—	2938	—	5-Nitro-2-furaldehyde-2(2'-hydroxy-ethyl semicarbazone)	$N_4O_5C_8H_{10}$	67
67574	26327	—	Leurocristine, sulfate (1:1) (vincristine)	$N_2O_{10}C_{46}H_{58} \cdot H_2SO_4$	15
80087	30053	443-30-1	*p*-Toluidine, α-iden-1-ylidene-*N,N*-dimethyl-	$NC_{10}H_{17}$	55
86016	9980	—	Copper oxide sulfate, hydrate	$3CuO \cdot CuSO_4 \cdot HOH$	—
92859	29831	—	Arsenic oxide	As_2O_3	—
109229	30000	—	L-Asparaginase	Unknown	52,80
140865	19272	—	*p*-Benzoquinone, 2-(3,7,11,15,19,23,27,31,35,39-decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl)-5,6-dimethoxy-3-methyl- (coenzyme Q10)	$O_4C_{59}H_{90}$	2
401593	14071	11018-96-5	Picropodophyllin, β-D-glucoside	$O_{13}C_{28}H_{32}$	45
509565	9565	—	Urea, 1-(2-[(2-aminoethyl) amino]ethyl)-3-phenyl-2-thio-	$N_4SC_{11}H_{18}$	11
509583	9583	5634-27-5	Dodecanamide, *N*-amidino-	$N_2OC_{13}H_{27}$	11
521828	21828	6464-78-4	N^2(*N*-Carboxy-3-phenyl-L-alanyl)-N^5-nitro-amidino-L-ornithine, *N*-benzyl ester	$N_6O_7C_{23}H_{28}$	1
522558	22558	—	2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-, 1,1-dioxide	$N_3O_4S_2ClC_7H_6$	2
522600	22600	—	Nicotinamide, 6-acetamido-	$N_2O_2C_8H_9$	100
522679	22679	—	6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	$N_3O_4S_2C_7H_6$	2

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
523313	23313	—	Aniline, 2,2′-bis(chloroarsylene)-	$N_2AsClC_{12}H_{12}$	79
523314	23314	—	Arsine, chlorobis(*o*-nitrophenyl)-	$N_2O_4AsClC_{12}H_8$	79
523316	23316	91-71-4	Benzoic acid, 2,2′-[(*p*-ureidophenyl) arsylenedithio]di-	$N_2O_5S_2AsC_{21}H_{17}$	79
523484	23484	3114-98-5	1,4-Naphthoquinone, 2-bromo-3-(phenylthio)-	$O_2SBrC_{16}H_9$	79
523485	23485	26037-62-7	1,4-Naphthoquinone, 2-bromo-3-(methylthio)-	$O_2SBrC_{11}H_7$	79
523486	23486	—	1,4-Naphthoquinone, 2,3-bis(methylthio)-	$O_2S_2C_{12}H_{10}$	79
524784	24784	25212-18-4	Arginine, polymer	$(N_4O_2C_6H_{12})n$	101
525020	25020	16164-66-2	2-Pyridineethanol, α-cyclopropyl-α-(*p*-methoxyphenyl)-β-phenyl-	$NO_2C_{23}H_{23}$	1
525442	25442	—	Propionamide, *N*-(*p*-chloro-α,α-dimethylphenethyl)-	$NOClC_{12}H_{16}$	100
525602	25602	3750-26-3	5-Hexeneamide, 5-acetamido-4-oxo- (primocarcine)	$N_2O_3C_8H_{12}$	83
525661	25661	—	Flammulin	Unknown	2
525816	25816	1013-59-8	3-Pyrrolin-2-one, 3-acetyl-5-*sec*-butyl-4-hydroxy- (tenuazonic acid)	$NOC_{10}H_{15}$	2
526318	26318	—	Salicyclic acid, 4-[(5-bromosalicylidene) amino]-	$NO_4BrC_{14}H_{10}$	51
526376	26376	32739-71-2	D-Glucosylamine, *N*-(*p*-methoxyphenyl)-	$NO_6C_{13}H_{19}$	72
526739	26739	78-60-4	2,5-Hexanediol, cyclic borate	$NO_2BC_8H_{13}$	24
526741	26741	26248-41-9	Tolyl borate, mixt. of isomers	$O_3BC_{21}H_{21}$	24
527179	27179	50-35-1	Phthalimide, *N*-(2,6-dioxo-3-piperidyl-	$N_2O_4C_{13}H_{10}$	18
527516	27516	736-26-5	Isonicotinic acid, 2-(4-nitroso-7-oxo-1,3,5-cycloheptatrien-1-yl) hydrazide	$N_4O_3C_{13}H_{10}$	79
527517	27517	—	Isonicotinic acid, 2-(4-nitroso-7-oxo-1,3,5-cycloheptatrien-1-yl) hydrazide, 1-oxide	$N_4O_4C_{13}H_{10}$	79
—	127	—	Stilbene, 4,4′-diamidino, di-isethionate	$N_4C_{18}H_{16}\cdot 2O_4SC_2H_6$	2
—	1185	—	1-(2-Methyl-4-chlorophenylazo) biguanide	$N_7ClC_9H_{12}$	8
—	1380	—	Ethylenediamine tetraacetic acid	$N_2O_8C_{10}H_{16}$	2
—	1577	—	5-Isopropyl-1-aza-3,7,-dioxabicyclo(3.3.0)-octane	$NO_2C_9H_{15}$	40
—	1866	—	Jalapin	$O_{16}C_{34}H_{56}$	2
—	2153	—	6-Chloro-9-(1′-D-dulcityl) isoalloxazine	$N_4O_7ClC_{16}H_{17}$	2
—	2516	—	2,4,6-Trichloroquinazoline	$N_2Cl_3C_8H_3$	6
—	3589	—	Calcium chloride	$CaCl_2$	—
—	5490	—	1,2-Bis(*p*-aminophenyl)-2-methylpropanone-1	$N_2OC_{16}H_{18}$	73
—	7396	—	Ether, 6-fluorohexylmethyl-	OFC_7H_{15}	66
—	7397	—	5-Fluoropentanol	OFC_5H_{11}	66
—	7837	—	1-Isonicotinyl-2-isopropylhydrazine dihydrochloride	$N_3OC_9H_{13}\cdot 2HCl$	5
—	8125	—	Tryptophan	$N_2O_2C_{11}H_{12}$	—
—	8327	—	1-Dimethylamino-2-allyoxy ethane	NOC_7H_{15}	21
—	8800	—	Benzenediazonium, *p*-anilino-, tetrafluoroborate-(1-)	$N_3C_{12}H_{10}\cdot BF_4$	26
—	13459	—	6,7-Dimethyl-9-(2′-acetoxyethyl) isoalloxazine	$N_4O_4C_{16}N_{16}$	10
—	13808	—	*p*-Nitrobenzenediazoaminoazobenzene	$N_6O_2C_{18}H_{14}$	76
—	16395	—	Carbamic acid, D-ribosyl-, ethyl ester	$NO_6C_8H_{15}$	47
—	16683	—	2-Benzimidazolinone, 5-*tert*-butyl-	$N_2OC_{11}H_{14}$	2
—	16866	—	Benzimidazolone, 1-methyl-3-(β-diethylaminoethyl)-, perchlorate	$N_3OC_{14}H_{21}\cdot HCl\ O_4$	2
—	18134	—	Propanol, 2,3-dimercapto-, bismuth salt	$OS_2C_3H_6\cdot \frac{2}{3}Bi$	71
—	18999	—	4,5-Imidazoledicarboxamide	$N_4O_2C_5H_6$	2
—	19121	—	Lutrexin	—	44
—	19548	—	3-Triazenecarboxanilide, 1,3-bis(*p*-chlorophenyl)-	$N_4OCl_2C_{13}H_{11}$	76
—	19549	—	Butyranilide, *N*-phenylazo-	$N_3OC_{16}H_{17}$	76
—	19918	—	β-Amylose triiodide	—	46
—	20497	—	Tryptamine, 5-hydroxy-, creatinine sulfate, monohydrate complex	$C_{14}H_{19}N_5O_2\cdot H_2SO_4\cdot H_2O$	—

TABLE A.—List of compounds*—Continued

NSC No.	Sloan-Kettering (SK) No.	CAS reg. No.	Compound	Molecular formula	Source†
—	20547	—	Cyclopentane carboxylic acid, 1-amino-, octyl ester-, hydrochloride	$NO_2C_{14}H_{27}\cdot HCl$	2
—	20845	—	Insulin	—	—
—	20890	—	Mercury-hematoporphyrin complex, disodium salt	$N_4O_6HgC_{34}H_{34}\cdot Na$	85
—	21509	—	Neocitol	—	74
—	22388	—	5-Amino-3,4-dicyano-1-pyrazolecarboxamide	$N_5OC_6H_4$	16
—	22841	—	Amylose triiodide	—	46,75
—	26744	—	Hexylene glycol borate, oleylamine salt	$NO_3BC_{24}H_{50}$	24
—	28239	—	7-Hydroxy-9α-methoxymitosane	$N_3O_6C_{16}H_{17}$	80
—	28265	—	1-Hydroxy-2-amino-7-aminomitosene	$N_4O_5C_{14}H_{16}$	80
—	29857	—	Magnesium carbonate	$MgCO_3$	—

*Data for individual compounds obtained from more than one source were pooled as the results did not vary in samples from different sources.

†See below.

Source of Chemicals*

Code	Source	Code	Source
1	Parke, Davis and Co. Ann Arbor, Mich	16	E. T. Du Pont de Nemours and Co. Wilmington, Del
2	Merck, Sharp and Dohme Rahway, NJ	17	Abbott Laboratories North Chicago, Ill
3	The Squibb Institute for Medical Research New Brunswick, NJ	18	The William S. Merrell Co. Cincinnati, Ohio
4	American Cyanamid Co. New York, NY	19	Schering Corporation Bloomfield, NJ
5	Hoffmann-LaRoche, Inc. Nutley, NJ	20	Bristol Laboratories Syracuse, NY
6	Wellcome Research Laboratories Research Triangle, NC	21	Rohm and Haas Co. Bristol, Pa
7	The John L. Smith Memorial for Cancer Research Chas. Pfizer and Co., Inc. Maywood, NJ	22	Baxter Laboratories, Inc. Morton Grove, Ill
8	American Cyanamid Co. Lederle Laboratories Division Pearl River, NY	23	University of Chicago Toxicity Laboratory Chicago, Ill
9	Mead Johnson and Co. Evansville, Ind	24	Standard Oil of Ohio Cleveland, Ohio
10	The Upjohn Co. Kalamazoo, Mich	25	S. B. Penick and Co. New York, NY
11	Eastman Kodak Co. Rochester, NY	26	Remington Rand, Inc. South Norwalk, Conn
12	Merck Frosst Laboratories Montreal, Canada	27	Wallace Laboratories, Inc. Cranbury, NJ
13	Chemical Biological Coordination Center National Research Council Washington, DC	28	Southern Research Institute Birmingham, Ala
14	CIBA-GEIGY Ardsley, NY	29	Drug Research and Development National Cancer Institute National Institutes of Health Bethesda, Md
15	Lilly Research Laboratories Eli Lilly and Co. Indianapolis, Ind	30	Sterling-Winthrop Research Institute Rensselaer, NY
		31	Warner-Lambert Research Institute Morris Plains, NJ

TABLE A.—List of compounds*—Continued

Code	Source
32	National Aniline Division Allied Chemical and Dye Corp. New York, NY
33	The New York Botanical Garden Bronx, NY
34	Schwarz Laboratories, Inc. Mt Vernon, NY
35	American Cancer Society Special Testing Program New York, NY
36	Mellon Institute Pittsburgh, Pa
37	The Glidden Co. Chicago, Ill
38	Schenlabs Pharmaceuticals, Inc. New York, NY
39	Ives Cameron Co. New York, NY
40	Commercial Solvents Corp. Terre Haute, Ind
41	Universal Detergents, Inc. Long Beach, Calif
42	Roussel Laboratories New York, NY
43	CIBA-GEIGY Summit, NJ
44	Hynson, Wescott and Co. Baltimore, Md
45	Sandoz Pharmaceuticals Hanover, NJ
46	IBC Research Laboratories, Inc. New York, NY
47	National Bureau of Standards Washington, DC
48	Delta Chemical Works, Inc. New York, NY
49	The Dow Chemical Co. Midland, Mich
50	The B. F. Goodrich Co. Research Center Brecksville, Ohio
51	Lever Brothers Co. Edgewater, NJ
52	Worthington Biochemical Corp. Freehold, NJ
53	Rockefeller Institute for Medical Research New York, NY
54	Dr. Selman A. Waksman Rutgers University New Brunswick, NJ
55	Dr. Carl T. Bahner Carson-Newman College Jefferson City, Tenn
56	Dr. Calvin L. Stevens Wayne State University Detroit, Mich
57	Dr. Roland K. Robins University of Utah Salt Lake City, Utah
58	Dr. C. S. Rondestvedt, Jr. E. I. DuPont de Nemours and Co. Wilmington, Del
59	Dr. Arthur Furst University of San Francisco San Francisco, Calif
60	Dr. Walter T. Smith, Jr. University of Kentucky Lexington, Ky
61	Dr. Donald Visser University of Southern California Los Angeles, Calif
62	Dr. John Ehrlich Parke, Davis and Co. Detroit, Mich
63	Dr. J. Reed Chemical Specialties Co., Inc. New York, NY
64	Mr. Henry N. Mitchell Sanford, Me
65	Dr. T. H. Jukes American Cyanamid Co. Princeton, NJ
66	Dr. F. L. M. Pattison University of Western Ontario London, Ontario
67	Dr. P. F. McLeod Eaton Laboratories Norwich, NY
68	Dr. Karl Dittmer The Petroleum Research Fund American Chemical Society Washington, DC
69	Dr. V. du Vigneaud Cornell University Medical College New York, NY
70	Dr. J. Philip Boston University Boston, Mass
71	Dr. E. A. H. Friedheim New York, NY
72	Dr. O. A. Runquist Hamline University St. Paul, Minn
73	Dr. R. Hertz National Cancer Institute Bethesda, Md
74	Mr. Frank A. Howard 30 Rockefeller Plaza New York, NY
75	Mr. H. A. Schaeffer Reed and Carnrick Pharmaceuticals Kenilworth, NJ

TABLE A.—List of compounds*—Continued

Code	Source
76	Dr. J. M. Ruegsegger Lederle Laboratories Division American Cyanamid Co. Pearl River, NJ
77	Frank W. Horner, Ltd. Montreal, Canada
78	Sloan-Kettering Institute personnel or related sources:
78–1	
78–3	
78–4	
78–5	
78–8	
78–12	
78–22	
78–23	
78–29	
78–30	
78–36	
78–44	
78–46	
79	Sankyo Co., Ltd. Tokyo, Japan
80	Kyowa Hakko Kogyo Co., Ltd. Tokyo, Japan
81	Takeda Chemical Industries, Ltd. Osaka, Japan
82	Fujisawa Pharmaceutical Co. Osaka, Japan
83	Japanese Foundation for Cancer Research Tokyo, Japan
84	Nippon Seibutsu Kagaku Saitama-ken, Japan
85	Daiichi Pharmaceutical Co. Tokyo, Japan
86	Dr. Hamao Umezawa National Institute of Health Tokyo, Japan
87	Dr. Fumiko Fukuoka National Cancer Center Research Institute Tokyo, Japan
88	Dr. Morizo Ishidate University of Tokyo Tokyo, Japan
89	Dr. K. Katagiri Shionogi Research Laboratory Shionogi and Co., Ltd. Osaka, Japan
90	Dr. Hiroaki Moriyama Sumitomo Chemical Co., Ltd. Osaka, Japan
91	Dr. Shinsuke Ose Dainippon Pharmaceutical Co., Ltd. Osaka, Japan
92	Dr. Toju Hata Kitasato University Tokyo, Japan
93	Dr. Koji Miura Kanazawa University Kanazawa, Japan
94	Dr. Yoshio Sakurai Cancer Institute Tokyo, Japan
95	Farbwerke Hoechst, A.G. Frankfurt (M), Germany
96	Farbenfabriken Bayer Wuppertal-Elberfield, Germany
97	Prof. Dr. Hermann Druckrey University of Freiburg Freiburg, Germany
98	Organisch-Chemische Anstalt de Universitat Basel Basel, Switzerland
99	Dr. Augusto De Barbieri Instituto Sieroteropico Milanese Milan, Italy
100	Dr. Giorgio Ferrari Simes S. p. a. Milan, Italy
101	Boots Pure Drug Co., Ltd. Nottingham, England
102	Chester Beatty Research Institute Royal Cancer Hospital London, England
103	Dr. F. E. Ray Cancer Research Laboratory University of Florida Gainesville, Fla

*All drugs were supplied directly to the Sloan-Kettering Institute for Cancer Research from the individual supplier and not through DR&D, Division of Cancer Treatment, NCI, unless specifically noted.

TABLE 1.—Criteria for evaluating tumor inhibition

Symbol	Degree of tumor inhibition	Tumor index*
–	None	0.76–1.00
±	Slight	0.51–0.75
+	Moderate	0.26–0.50
++	Strong	0.05–0.25
+++	Complete	0.0

*The tumor index was determined by dividing the average tumor diameter in the treated group by the average tumor diameter in the control group.

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				1. Alkylating Agents					
762	101	0.50	S*	−7/+27	3/10	0.27/1.85	0.15	++	++
762	101	0.25	S*	+22/+52	1/30	0.80/1.64	0.49	+	±
762	101	0.125	S*	+48/+53	0/5	1.69/1.99	0.85	–	–
762	101	0.0625	S*	+33/+52	0/5	1.71/1.99	0.86	–	–
10107	598	1.5	S*	−23/+49	1/20	0.0/1.69	0.0	+++	+++
9506	1424	5.0	PO	−19/+22	0/20	0.17/1.15	0.15	++	++
9506	1424	1.0	PO	−11/+36	0/5	0.70/1.68	0.42	+	±
8806	15673	1.0	S*	+52/+61	2/25	0.0/2.73	0.0	+++	+++
—	20598	1.0	S*	+62/+65	0/5	0.28/1.08	0.26	+	±
—	20597	1.0	S*	+67/+65	0/10	0.0/1.08	0.0	+++	+++
525691	25691	12.5	CMC	+23/+52	4/10	0.17/2.10	0.08	++	+++
526407	26407	25	CMC*	+26/+57	2/15	0.0/2.43	0.0	+++	+++
525823	25823	100	CMC*	−2.0/+6.5	0/10	0.0/2.24	0.0	+++	+++
525823	25823	50	CMC*	+31/+64	0/5	0.0/2.06	0.0	+++	+++
526622	26622	125	CMC*	−17/+61	0/10	0.07/2.05	0.03	++	++
525022	25022	200	CMC*	−21/+59	4/15	0.0/2.18	0.0	+++	+++
525022	25022	100	CMC*	+3/+45	2/15	1.46/2.02	0.14	++	+
526406	26406	25	CMC*	−10/+60	2/10	0.0/1.94	0.0	+++	+++
527453	27453	50	CMC*	−8/+49	1/10	0.20/1.97	0.10	++	+++
64928	25813	125	PO	+54/+63	1/10	2.18/2.00	1.09	–	–
62403	27456	1.0	CMC*	+38/+57	0/20	0.11/2.16	0.05	++	+++
62403	27456	0.5	CMC*	+45/+45	0/15	0.49/2.07	0.24	++	++
62403	27456	0.25	CMC*	+66/+61	0/10	0.64/1.60	0.40	+	±
23909	24464	20	S*	−2/+40	0/10	0.04/1.88	0.20	++	+++
409962	27702	8.0	S*	+12/+47	0/15	0.0/2.36	0.0	+++	+++
409962	27702	4.0	S*	+6/+34	0/20	0.27/1.33	0.20	++	++
409962	27702	2.0	S*	+29/+44	0/5	1.21/1.74	0.70	±	–
409962	27702	1.0	S*	+32/+42	0/5	1.27/2.26	0.56	±	–
527408	27408	1.25	S*	+26/+49	1/15	0.65/1.88	0.35	+	+++
26750	12066	250	S	+36/+42	1/5	1.41/1.33	1.06	–	–
41269	11088	60	CMC*	+36/+70	1/10	0.0/1.80	0.0	+++	+++
47774	24591	50	CMC*	+10/+61	2/10	0.28/1.88	0.15	++	++
47774	24591	25	CMC*	+44/+65	0/5	0.62/1.00	0.62	±	–
74437	13595	30	CMC*	+49/+52	0/5	0.53/0.94	0.56	±	–
17016	6699	250	CMC	+10/+36	1/5	1.77/1.50	1.18	–	–
17016	6699	100	CMC	+13/+60	0/20	1.40/1.76	0.80	–	–

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
750	5681	5.0	PO	+12/+55	4/20	0.67/1.54	0.44	+	±
750	5681	3.0	PO	+37/+58	1/10	1.35/1.34	1.01	−	−
3052	7505	100	PO	+24/+53	0/5	0.07/1.35	0.05	++	+++
3052	7505	50	PO	+18/+43	1/25	0.26/1.90	0.14	++	++
524469	24469	0.25	S	+31/+48	2/15	0.83/0.83	1.00	−	−
529213	29213	2.5	CMC	+24/+37	2/10	0.31/1.75	0.18	++	±
529213	29213	1.0	CMC	+17/+44	0/5	0.61/2.11	0.29	+	−
3094	11687	50	PO	+2/+47	2/10	0.87/1.03	0.84	−	−
3094	11687	25	PO	+45/+50	2/10	0.94/0.97	0.97	−	−
408428	14405	125	CMC	+28/+40	1/10	0.83/0.93	0.89	−	−
—	15749	250	PO	+34/+43	1/10	1.12/1.14	0.98	−	−
49421	4614	1.0	S*	+33/+46	1/15	0.16/1.55	0.10	++	++
9717	3818	1.0	S	+13/+49	2/11	0.22/1.55	0.14	++	++
26271	20501	25	S*	+3/+55	7/25	0.18/1.91	0.09	++	+++
26271	20501	12.5	S*	+13/+65	0/10	0.22/1.81	0.12	++	+++
26271	20501	6.25	S*	+37/+67	0/10	0.19/1.94	0.10	++	+++
520644	20644	25	CMC*	+17/+54	1/10	0.0/1.48	0.0	+++	+++
520644	20644	10	CMC*	+25/+77	0/10	0.0/2.00	0.0	+++	+++
520645	20645	50	CMC*	+30/+56	1/5	0.11/1.61	0.07	++	++
520645	20645	25	CMC*	+49/+66	0/10	0.27/1.48	0.18	++	++
520645	20645	12.5	CMC*	+65/+63	0/10	1.08/1.92	0.56	±	−
520646	20646	15	CMC*	+54/+76	1/10	0.0/1.77	0.0	+++	+++
520647	20647	20	CMC*	+56/+76	0/10	0.28/1.77	0.16	++	++
42158	17360	20	S*	+44/+43	3/10	0.05/0.91	0.06	++	+++
—	15385	2.5	S*	−3/+29	2/5	0.30/0.84	0.36	+	±
9706	1133	0.5	S*	+11/+36	0/5	0.14/1.00	0.14	++	+++
9706	1133	0.25	S*	+1/+40	0/10	0.27/1.39	0.19	++	+++
9706	1133	0.125	S*	+47/+55	2/20	0.0/1.58	0.0	+++	+++
9706	1133	0.0625	S*	+53/+62	1/30	0.46/1.74	0.26	+	±
9706	1133	0.0312	S*	+71/+67	0/10	1.08/1.88	0.57	±	−
6396	6882	4.0	S*	−25/+32	4/10	0.0/1.57	0.0	+++	+++
6396	6882	2.0	S*	+10/+46	1/10	0.0/1.43	0.0	+++	+++
6396	6882	1.0	S*	+8/+28	1/15	0.0/1.26	0.0	+++	+++
6396	6882	0.5	S*	+67/+72	0/10	0.69/2.35	0.29	+	±
528988	28988	10	CMC	+5/+31	2/10	0.0/1.97	0.0	+++	+++
48225	4383	1.0	S*	−22/+37	2/10	0.0/2.00	0.0	+++	+++
48225	4383	0.5	S*	+22/+44	3/25	0.21/1.56	0.13	++	++
48225	4383	0.25	S*	+46/+44	3/10	0.41/1.47	0.28	+	+
				II. Pyrimidine Analogs					
19893	18143	25	S	+30/+47	1/15	0.57/1.44	0.40	+	±
19893	18143	17.5	S	+46/+59	0/10	0.63/0.86	0.73	±	−
3425	13056	250	CMC	+51/+50	0/5	0.79/0.75	1.05	−	−
529351	29423	50	CMC	+38/+44	0/5	1.74/2.29	0.76	−	−
1589	11770	250	S	+23/+63	0/5	1.33/1.54	0.86	−	−
146604	19273	2.5	S	+61/+58	1/5	1.44/1.66	0.87	−	−
27640	19150	40	S	+37/+53	2/25	1.20/1.72	0.70	±	−
67670	20298	125	CMC	+14/+67	2/10	0.55/1.33	0.41	+	−
31712	18354	20	S	+41/+42	0/5	1.49/1.20	1.24	−	−
3061	5051	10	CMC	+48/+58	0/10	1.41/1.34	1.05	−	−
3062	5266	25	CMC	−8/+54	2/5	1.22/1.36	0.90	−	−
3062	5266	10	CMC	+29/+58	3/10	1.14/1.34	0.85	−	−
—	29511	60	CMC	+14/+22	1/5	1.79/1.84	0.97	−	−
—	29217	50	CMC	+29/+43	0/5	1.38/2.04	0.68	±	−
48006	20000	25	S	+23/+55	2/10	0.28/1.59	0.18	++	+

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
48006	20000	10	S	+25/+62	2/10	0.35/1.60	0.22	++	+
—	6883	2.0	S	+63/+54	0/10	1.47/1.68	0.88	−	−
				III. Purines and Analogs					
14666	1387	100	GA	+30/+41	0/5	2.16/2.38	0.91	−	−
3702	1493	125	CMC	+37/+41	0/10	2.21/2.38	0.93	−	−
14664	1494	250	GA	+37/+47	1/10	2.36/3.14	0.75	±	−
110037	17359	50	CMC	+41/+38	0/5	2.38/2.13	1.12	−	−
527612	27612	10	CMC	+23/+38	0/5	1.92/2.13	0.90	−	−
528403	28403	35	A+C	+29/+38	0/5	2.13/2.13	1.00	−	−
749	1150	200	CMC	−1/+22	0/10	1.37/1.59	0.86	−	−
749	1150	75	CMC	+22/+48	1/20	1.21/1.35	0.90	−	−
756	1149	250	GA	+46/+56	1/10	1.33/1.62	0.82	−	−
—	19994	10	S	+66/+60	1/5	1.90/1.29	1.47	−	−
753	8709	250	S	−6/+34	4/20	0.50/1.38	0.36	+	±
744	6048	150	CMC	+37/+53	0/10	0.82/1.71	0.48	+	−
77640	7347	25	CMC	+14/+56	2/20	0.59/1.52	0.39	+	±
48716	25532	50	CMC*	+50/+55	2/5	1.30/1.42	0.92	−	−
45153	25533	100	CMC*	+13/+55	1/5	1.24/1.42	0.87	−	−
39336	25531	20	CMC*	+47/+55	0/5	1.88/1.42	1.32	−	−
513473	13473	100	S	+65/+64	0/5	0.92/1.49	0.62	±	−
25650	14944	100	S	+37/+59	1/5	1.30/1.60	0.81	−	−
526180	26180	60	CMC*	+28/+37	1/5	1.43/1.65	0.87	−	−
526485	26485	60	PO	+13/+53	2/15	0.25/1.71	0.15	++	++
528837	28837	10	A+C	0/+37	1/5	1.25/1.71	0.73	±	−
755	5357	50	CMC	−3/+50	1/5	0.27/1.65	0.16	++	++
755	5357	35	CMC	+5/+57	3/10	0.48/1.91	0.25	++	+
755	5357	30	CMC	+34/+52	0/15	0.46/1.84	0.25	++	+
755	5357	20	CMC	+28/+49	2/25	0.53/1.46	0.36	+	±
755	5357	15	CMC	+46/+52	0/10	0.84/1.89	0.44	+	±
38887	20355	10	CMC	+45/+64	0/10	0.41/1.52	0.27	+	±
39084	20354	100	CMC	+26/+68	1/10	0.07/1.34	0.05	++	+
743	1395	60	S	+29/+52	2/15	1.24/1.34	0.93	−	−
752	5459	3.0	CMC	+13/+55	0/15	0.86/1.22	0.70	±	−
43405	13470	15	CMC	+44/+56	0/5	1.63/1.43	1.14	−	−
58385	14377	15	CMC	+34/+35	2/5	0.13/0.83	0.16	++	++
58385	14377	10	CMC	+39/+46	1/15	0.40/1.04	0.39	+	++
759	1509	125	S	+44/+52	0/10	1.47/1.34	1.10	−	−
25652	17902	250	CMC	+3/+41	2/5	1.66/1.45	1.14	−	−
3057	1054	50	GA	+35/+34	1/5	1.03/1.00	1.03	−	−
25165	18094	100	S	+19/+45	2/5	0.73/1.09	0.67	±	−
25165	18094	50	S	+84/+60	1/5	1.36/1.29	1.05	−	−
4911	12355	125	CMC	+35/+58	0/10	0.18/1.73	0.10	++	++
520950	20950	50	PO	+54/+71	0/5	1.36/1.76	0.77	−	−
29422	18615	5.0	CMC	+29/+40	0/5	0.83/0.93	0.89	−	−
29422	18615	2.5	CMC	+36/+65	1/5	1.05/0.94	1.12	−	−
—	4901	250	GA	+40/+49	0/5	1.96/1.73	1.13	−	−
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+19/+53	5/25	1.58/1.47	1.07	−	−
742	9505	2.0	S*	+16/+54	2/10	1.26/1.68	0.75	±	−
742	9505	1.0	S*	+53/+62	0/10	1.24/1.78	0.70	±	−
7365	13835	0.1	S*	+5/+50	2/10	1.47/1.44	1.02	−	−
7365	13835	0.05	S*	+40/+52	0/5	0.89/1.15	0.77	−	−
3063	591	75	CMC	+42/+52	1/10	1.65/1.35	1.22	−	−

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
1393	13148	15	CMC	+10/+48	1/5	1.32/1.60	0.83	–	–
5197	13640	5.0	CMC	+46/+35	1/5	0.85/1.00	0.85	–	–
—	1833	400	CMC	−6/+37	1/5	1.30/1.36	0.96	–	–
—	1833	200	CMC	+2/+39	2/10	1.22/1.51	0.81	–	–
—	1833	100	CMC	+25/+50	0/5	1.60/1.97	0.81	–	–
3073	642	50	S*	+21/+26	0/20	1.24/1.19	1.04	–	–
3073	642	100	S*	+33/+36	0/10	1.73/1.56	1.11	–	–
739	1072	0.25	S*	+44/+62	0/10	1.32/1.22	1.08	–	–
740	1275	1.5	S*	+10/+39	1/5	1.68/2.01	0.84	–	–
740	1275	1.0	S*	+18/+33	2/20	0.87/1.01	0.86	–	–
740	1275	0.5	S*	+30/+64	3/20	1.85/1.86	0.99	–	–
740	1275	0.25	S*	+40/+71	0/5	1.90/1.76	1.08	–	–
—	1332	50	S*	+18/+21	2/15	1.39/1.46	0.95	–	–
—	1418	1000	GA	+47/+58	1/10	1.10/1.17	0.94	–	–
—	1418	500	GA	+53/+50	0/10	1.50/1.56	0.96	–	–
				V. Steroids					
49420E	2795	50	CMC	+45/+29	1/10	1.55/1.28	1.21	–	–
49420E	2795	37.5	CMC	+26/+34	1/10	1.91/1.80	1.06	–	–
49420E	2795	25	CMC	+25/+14	1/5	1.72/1.39	1.24	–	–
10483E	3047	37.5	CMC	+26/+50	0/5	1.25/1.52	0.82	–	–
10483E	3047	25.0	CMC	+65/+50	2/10	1.30/1.56	0.83	–	–
12600E	15347	1.5	CMC	+15/+31	2/10	0.60/1.52	0.39	+	–
9166E	2799	500	CMC	+51/+57	0/25	1.95/2.01	0.97	–	–
9565E	2931	375	CMC	+59/+40	0/5	1.35/1.49	0.91	–	–
9564E	17653	500	CMC	+35/+40	0/5	1.33/1.49	0.89	–	–
3351E	17469	375	CMC	+26/+55	0/5	1.26/1.60	0.79	–	–
10704E	16816	375	CMC	+43/+64	1/5	2.05/1.45	1.41	–	–
12198E	21102	500	CMC	+48/+61	1/5	1.90/2.14	0.89	–	–
—	2932	450	GA	+31/+41	0/5	1.29/1.52	0.85	–	–
—	3058	300	GA	+32/+42	0/5	1.37/1.52	0.90	–	–
—	3092	10	CMC	+21/+54	0/5	1.34/1.35	0.99	–	–
20293E	10696	40	CMC	+21/+62	2/10	1.51/1.32	1.14	–	–
20293E	10696	20	CMC	+14/+48	0/5	1.13/1.29	0.88	–	–
23759E	20379	500	CMC	+57/+61	0/5	2.25/2.14	1.05	–	–
				VI. Antibiotics					
402815+	2405	2000	S*	+55/+49	0/10	1.80/1.70	1.06	–	–
14083	4516	500	S	+56/+53	0/5	2.40/2.30	1.04	–	–
3069	2155	500	CMC*	+43/+50	0/10	1.36/1.27	1.07	–	–
3069	2155	400	CMC*	+50/+53	0/5	1.90/2.30	0.83	–	–
13252	1333	50	GA*	+25/+42	0/10	1.50/1.42	1.06	–	–
9169	2859	150	S	+27/+42	0/6	1.29/1.42	0.91	–	–
185	903	1.0	S	+12/+53	3/15	0.65/1.50	0.43	+	±
17257	17442	0.5	S	+32/+67	1/10	0.72/2.05	0.35	+	±
44690	1039	7.5	S	+32/+77	1/5	2.05/2.04	1.00	–	–
—	2163	12.5	CMC	+36/+50	1/5	1.53/1.44	1.06	–	–
3067	2662	15	CMC	−8/+28	0/10	1.51/1.26	1.20	–	–
—	2935	0.25	S	+3/+35	1/5	1.14/1.65	0.69	±	–
400978	4996	0.5	S	+25/+54	0/5	1.13/1.44	0.78	–	–
9168	6258	10	CMC	+30/+40	0/5	0.61/0.80	0.76	–	–
9168	6258	5.0	CMC	+52/+52	2/10	0.99/0.93	1.06	–	–
58368	13617	50	CMC*	+32/+48	0/5	1.66/1.81	0.92	–	–
—	862	0.025	S	+23/+58	0/5	0.96/1.34	0.72	±	–
18268	11822	0.025	A+S	+77/+73	1/5	2.40/2.05	1.17	–	–

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
3053	14095	0.05	A+S	+50/+54	1/5	1.24/1.21	1.02	−	−
3053	14095	0.025	A+S	+49/+57	0/15	1.59/1.37	1.16	−	−
	2662	15	CMC	−8/+28	0/10	1.51/1.26	1.20	−	−
14347	12772	250	S*	+48/+43	2/5	0.95/1.10	0.86	−	−
26980	19256	1.0	S	+2/+59	1/25	0.14/1.69	0.08	++	++
26980	19256	0.5	S	+29/+96	0/5	0.45/2.22	0.20	++	±
26980	19256	0.25	S	+46/+96	0/5	1.40/2.22	0.63	±	−
—	20779	2.0	S	+36/+42	0/10	0.0/1.33	0.0	+++	+++
—	28008	2.5	S	+2/+52	4/15	0.02/1.79	0.01	++	+++
—	28008	1.25	S	−9/+61	1/5	0.0/1.57	0.0	+++	+++
—	28009	1.25	A+S	+18/+54	0/10	0.0/1.61	0.0	+++	+++
—	28010	2.5	S	−9/+49	1/10	0.0/1.86	0.0	+++	+++
—	28145	2.5	A+S	+51/+50	0/10	2.01/1.86	1.08	−	−
—	28146	5.0	A+S	0/+57	1/5	0.0/1.64	0.0	+++	+++
—	28146	2.5	A+S	+28/+48	2/10	0.0/1.63	0.0	+++	+++
—	28242	5.0	A+S	+33/+52	1/10	0.06/1.48	0.04	++	+++
—	28242	2.5	A+S	+33/+47	0/5	0.33/1.32	0.25	++	++
524678	24678	2.0	S	+27/+65	0/5	1.00/0.80	1.25	−	−
524678	24678	1.0	S	+30/+59	0/5	1.34/1.88	0.71	±	−
524678	24678	0.5	S	+57/+60	0/5	2.16/2.35	0.92	−	−
3055	12414	50	S	+24/+69	0/5	1.03/1.44	0.72	−	−
—	19439	500	S	+62/+70	0/5	1.96/2.13	0.92	−	−
58514	20863	2.0	S*	+45/+61	1/10	1.48/2.15	0.69	±	−
58514	20863	0.05	S*	+10/+41	1/5	1.51/2.06	0.73	±	−
58514	20863	0.025	S*	+15/+45	1/10	2.16/2.25	0.96	−	−
58856	25707	1.25	A+W	+52/+42	2/5	1.78/1.71	1.04	−	−
526417	26417	0.025	A+S	+62/+56	2/10	1.63/1.97	0.73	−	−
526094	26094	0.005	A+S	+63/+56	1/10	2.06/1.97	1.04	−	−
525822	25822	0.005	A+S	+47/+61	2/15	1.89/2.19	0.86	−	−
525822	25822	0.0025	A+S	+35/+61	2/10	2.22/2.20	1.01	−	−
24559	20047	0.3	S	+44/+63	0/5	0.98/1.62	0.60	±	−
52947	27773	1.0	S*	+45/+59	0/5	2.20/1.88	1.17	−	−
83340	28487	5.0	S	+11/+56	3/20	1.39/1.97	0.71	±	−
59729	28430	0.5	S	+12/+64	0/5	0.98/2.06	0.48	+	−
59729	28430	0.25	S	−13/−47	1/5	1.33/2.28	0.59	±	±
65423	9749	5.0	S	+50/+53	1/5	0.93/1.19	0.78	−	−
76029	13328	2500	S	+43/+52	1/5	1.95/1.55	1.26	−	−
76029	13328	500	S	+54/+56	0/10	1.21/1.27	0.95	−	−
39147	20250	0.3	S	+25/+66	1/5	0.53/1.84	0.29	+	±
39147	20250	0.15	S	+21/+58	1/5	0.98/1.86	0.53	±	±
45383	20556	0.2	A+S	0/+74	2/10	0.77/2.11	0.36	+	−
45383	20556	0.1	A+S	+9/+76	0/5	1.49/1.92	0.78	−	−
45383	20556	0.05	A+S	+44/+67	0/5	1.15/1.55	0.74	±	−
53104	21568	500	CMC	+23/+56	1/5	1.55/1.84	0.84	−	−
521778+	21778	500	S	+54/+67	0/5	1.85/1.82	1.02	−	−
31083	21721	1000	S	+37/+64	2/10	1.33/1.85	0.72	±	−
31083	21721	500	S	+41/+35	1/5	1.05/1.55	0.68	±	−
526368	26368	1.0	CMC	+52/+52	0/10	1.85/1.84	1.01	−	−
—	18355	0.05	S*	+49/+44	2/5	1.12/1.00	1.12	−	−
51812	24907	80	CMC*	+29/+51	2/5	1.57/1.87	0.84	−	−
526598	26598	0.25	CMC	+55/+64	0/10	1.38/1.32	1.05	−	−
56410	25021	0.025	S	+57/+50	1/15	1.54/2.03	0.76	−	−
				VII. Quinolines					
4141	11874	50	CMC	+41/+61	0/5	1.30/1.05	1.24	−	−

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
528997	28997	12.5	CMC	+40/+43	0/5	2.01/1.93	1.04	–	–
528995	28995	25	CMC	+33/+43	0/5	1.50/1.93	0.78	–	–
528996	28996	2.5	CMC	+35/+43	0/5	1.64/1.93	0.85	–	–
19645	16292	2.5	CMC	+43/+40	0/10	1.23/1.22	1.01	–	–
—	16293	8.0	CMC	−14/+53	2/5	1.05/1.32	0.80	–	–
—	16293	4.0	CMC	+44/+40	0/5	1.14/1.22	0.93	–	–
				VIII. Miscellaneous Compounds					
757	280	0.50	S	+21/+67	0/10	1.19/1.05	1.13	–	–
757	280	0.25	S	+6/+28	0/5	1.66/1.40	1.19	–	–
9170	15025	20	S	+23/+49	1/5	1.50/1.37	1.09	–	–
9170	15025	10	S	+50/+71	0/10	1.63/1.99	0.82	–	–
—	19121	10	CMC	+44/+65	0/5	1.03/0.94	1.10	–	–
—	21509	250	S	+57/+57	0/5	1.80/1.30	1.38	–	–
13875	1905	125	CMC*	+68/+70	1/5	1.71/1.53	1.12	–	–
525816	25816	50	S	+45/+73	1/5	2.10/1.71	1.23	–	–
509583	9583	1.0	S	+36/+47	1/5	1.52/1.48	1.03	–	–
4	3844	200	CMC	+25/+53	1/5	2.00/1.87	1.07	–	–
4	3844	50	CMC	+47/+54	0/5	1.19/1.03	1.15	–	–
36390	436	4.0	GA	+13/+45	1/5	0.97/0.98	0.99	–	–
36390	436	2.0	GA	+9/+45	0/5	1.09/0.98	1.11	–	–
4794	1356	15	S	−7/+49	0/5	1.60/1.49	1.07	–	–
4794	1356	5.0	S	+54/+60	0/5	1.73/1.66	1.04	–	–
14574	1471	50	S	+36/+50	0/5	1.80/1.52	1.18	–	–
—	1866	10	CMC	+40/+60	0/5	1.53/1.66	0.92	–	–
67574	26327	0.25	S	−15/+36	2/10	0.90/1.98	0.45	+	–
67574	26327	0.125	S	+9/+42	0/5	1.79/2.26	0.79	–	–
64075	9112	100	CMC	+18/+50	2/5	0.84/1.00	0.84	–	–
64074	9113	100	CMC	+35/+50	1/5	0.96/1.05	0.91	–	–
12865	11258	125	CMC	+60/+55	1/5	0.66/0.93	0.71	±	–
33963	18766	30	CMC	+19/+68	1/5	1.74/1.83	0.95	–	–
4730	14406	37.5	S	+46/+46	0/5	1.57/1.49	1.05	–	–
—	1577	100	PG	+51/+45	1/5	1.31/1.29	1.02	–	–
59354	25627	250	CMC	+35/+49	1/10	1.06/1.87	0.57	±	–
5354	1147	200	S*	+31/+64	3/10	1.53/1.80	0.85	–	–
5354	1147	50	S*	+66/+75	0/5	1.69/1.39	1.22	–	–
—	20547	50	CMC	+50/+67	0/5	1.75/1.82	0.96	–	–
25602	25602	12.5	S	+8/+73	1/5	1.10/1.36	0.81	–	–
527516	27516	25	CMC	+7/+45	2/10	1.75/1.66	1.05	–	–
66248	26071	100	CMC*	+48/+62	1/10	0.18/2.39	0.08	++	++
53582	25513	62.5	CMC*	+18/+50	0/10	0.0/1.22	0.0	+++	+++
53582	25513	31.25	CMC*	+27/+58	1/10	0.49/1.91	0.26	+	+
9242	25515	15.63	CMC*	+56/+66	0/5	2.01/2.53	0.79	–	–
49403	25512	125	CMC	+31/+56	2/5	1.11/1.45	0.77	–	–
—	1380	125	CMC	+50/+42	1/5	1.55/1.20	1.29	–	–
—	16683	125	CMC	+34/+54	1/10	0.84/1.20	0.70	±	–
23306	26081	60	CMC*	+30/+48	0/5	1.26/1.03	1.22	–	–
2100	384	250	GA	+37/+50	1/5	1.81/1.49	1.22	–	–
2100	384	50	GA	+20/+44	0/10	1.58/1.27	1.24	–	–
—	2938	50	GA	+53/+49	1/5	1.60/1.49	1.07	–	–
522558	22558	500	CMC	+38/+56	0/5	0.98/1.61	0.61	±	–
25647	2401	10	CMC	+71/+70	2/5	2.23/1.53	1.46	–	–
34540	24297	150	S	+30/+65	0/10	1.52/1.34	1.13	–	–
—	18999	25	CMC	+47/+31	1/5	0.94/1.52	0.62	±	–
—	22388	200	CMC	+33/+69	4/15	1.57/2.12	0.75	±	–

TABLE 2.—Effect of compounds on Flexner-Jobling carcinoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
36539	24298	160	CMC	+29/+63	2/10	2.25/2.11	1.07	–	–
45409	24299	80	CMC	+49/+64	3/15	1.49/2.05	0.73	±	–
45409	24299	40	CMC	+63/+57	0/5	2.44/2.36	1.03	–	–
527517	27517	10	CMC	+13/+52	1/5	2.40/2.00	1.20	–	–
31659	19453	0.5	S	+64/+68	0/5	1.42/1.96	0.72	±	–
—	12356	10	CMC	+41/+62	1/10	1.30/1.78	0.73	±	–
523485	23485	7.5	CMC	+34/+55	1/5	1.61/1.58	1.02	–	–
523484	23484	15	CMC	+16/+66	1/5	1.52/1.93	0.79	–	–
523486	23486	4.0	CMC	+20/+66	0/5	1.74/1.93	0.90	–	–
758	1812	1500	S	+37/+54	1/10	1.58/1.27	1.24	–	–
758	1812	750	S	+51/+46	0/10	1.08/1.43	0.76	–	–
17559	22575	250	CMC	+62/+70	1/5	2.10/2.07	1.01	–	–
—	19918	250	S	+42/+61	1/5	2.02/1.51	1.34	–	–
—	16395	100	S*	+62/+66	1/5	1.65/1.44	1.15	–	–
24854	20895	1000	S	+51/+56	1/25	1.72/1.88	0.91	–	–
54186	24580	25	S*	+62/+60	0/15	1.67/1.60	1.04	–	–
524784	24784	2.0	S	+65/+68	0/5	1.77/1.48	1.20	–	–
—	8125	1000	S	+42/+37	0/5	2.17/2.08	1.04	–	–
7786	13943	50	S	−2/+66	1/5	1.65/1.44	1.15	–	–
751	5393	500	CMC	+20/+30	0/10	1.26/1.35	0.93	–	–
109229	30000	167 IU	S	+42/+39	0/10	1.49/1.71	0.87	–	–
35847	24759	125	S	+24/+42	1/5	2.19/1.71	1.28	–	–
35847	24760	8.0	CMC	+33/+65	0/5	2.11/2.42	0.87	–	–
35847	24760	4.0	CMC	+37/+48	0/5	1.04/1.03	1.01	–	–
38280	24761	16	S	+57/+73	1/5	1.39/1.36	1.02	–	–
527179	27179	1000	A+C*	+21/+42	0/10	2.07/1.61	1.29	–	–
748	7078	200	PG	+46/+54	0/5	1.82/1.42	1.28	–	–
748	7078	125	PG	+57/+33	0/5	1.31/1.72	0.76	–	–
3051	8328	250	S	+17/+59	5/15	1.78/1.77	1.01	–	–
747	6479	750	PG	+48/+54	2/10	1.54/1.61	0.96	–	–
—	3501	500	S	+35/+30	1/10	1.21/1.51	0.80	–	–
32065	22591	100	CMC	+28/+50	0/5	1.87/1.52	1.23	–	–
3095	2917	75	S	+24/+30	0/10	1.43/1.51	0.95	–	–
746	129	1000	S	+6/+44	2/10	0.60/1.50	0.40	+	–
746	129	500	S	+22/+49	1/20	1.14/1.42	0.80	–	–
—	3687	500	S	+41/+43	0/5	1.72/1.68	1.02	–	–
—	3687	300	S	+57/+49	0/5	1.50/1.49	1.01	–	–
—	610	6.0	S	+50/+55	0/5	1.61/1.36	1.18	–	–
25649	8856	25	CMC	+50/+70	1/10	0.50/2.23	0.22	++	+
27223	16767	150	S*	+25/+24	0/5	1.26/1.00	1.26	–	–
—	8800	0.1	S*	+50/+56	0/5	1.52/1.58	0.96	–	–
526741	26741	62.5	PO	+22/+55	3/15	1.95/2.00	0.98	–	–
526741	26741	31.25	PO	+49/+48	0/5	1.89/1.68	1.13	–	–
526739	26739	62.5	PO	+38/+57	1/10	1.18/1.75	0.67	±	–
—	26744	15	PO	+31/+58	2/5	1.58/1.84	0.86	–	–
25648	5326	25	CMC	+68/+76	1/5	2.15/1.77	1.21	–	–
38583	1417	250	S	+57/+77	1/5	1.70/2.04	0.83	–	–
523316	23316	20	CMC	+56/+52	0/5	1.80/1.89	0.95	–	–
523314	23314	8.0	CMC	+68/+59	2/10	0.99/1.35	0.73	±	–
523313	23313	10	S	+20/+55	2/5	2.20/1.98	1.11	–	–
12693	23315	20	CMC	+55/+55	0/5	1.80/1.98	0.91	–	–
—	8327	150	S	+11/+54	3/10	1.10/1.61	0.68	±	–
3070	2800	10	CMC	+10/+42	2/25	0.89/1.02	0.87	–	–
3060	420	8.0	S	+52/+56	2/10	1.92/1.62	1.19	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				1. Alkylating Agents					
762	101	0.5	S*	+17/+60	1/10	0.16/2.63	0.06	++	++
762	101	0.25	S*	+13/+59	2/50	0.53/3.03	0.17	++	+
762	101	0.125	S*	+35/+77	0/5	2.50/3.38	0.74	±	−
762	101	0.0625	S*	+62/+77	0/5	2.47/3.38	0.73	±	−
10107	598	2.0	S*	−6/+56	2/5	1.68/3.83	0.44	+	−
10107	598	1.5	S*	−10/+42	2/10	1.68/3.37	0.50	+	−
9506	1424	5.0	PO	−26/+47	1/15	0.61/2.47	0.25	++	+
9506	1424	2.5	PO	−10/+40	1/10	0.58/1.40	0.41	+	−
9506	1424	1.0	PO	+4/+45	1/10	0.82/1.60	0.51	±	−
8806	15673	2.5	S*	+4/+38	1/5	0.29/4.14	0.07	++	++
8806	15673	2.0	S*	+19/+35	0/15	0.42/3.14	0.13	++	++
8806	15673	1.0	S*	+31/+53	3/35	0.59/2.98	0.20	++	++
14210	21739	2.0	CMC*	+41/+62	0/10	0.45/3.56	0.13	++	++
14210	21739	1.0	CMC*	+33/+63	0/5	0.82/3.04	0.27	+	±
—	20598	1.0	S*	+25/+55	0/10	0.43/3.20	0.13	++	++
—	20597	1.0	S*	+43/+52	0/10	0.54/2.92	0.18	++	++
525691	25691	12.5	CMC	+11/+56	3/25	1.04/2.80	0.23	++	±
526407	26407	25	CMC*	+16/+57	0/10	0.78/3.82	0.20	++	±
525823	25823	100	CMC*	−12/+59	0/10	0.32/1.44	0.22	++	++
525823	25823	50	CMC*	−5/+52	0/5	0.35/1.58	0.22	++	++
526622	26622	50	CMC*	+33/+45	0/10	0.58/2.30	0.25	++	±
525022	25022	100	CMC*	+3/+64	1/10	0.50/3.41	0.15	++	++
526406	26406	25	CMC*	+1/+64	2/10	0.67/2.52	0.26	+	±
527453	27453	50	CMC*	+12/+40	0/10	0.40/3.18	0.13	++	++
62403	27456	1.0	CMC*	+19/+37	0/15	1.00/3.93	0.25	++	±
62403	27456	0.5	CMC*	+38/+49	0/15	2.01/3.43	0.59	±	−
62403	27456	0.25	CMC*	+52/+56	0/5	3.35/4.36	0.77	−	−
46338	14913	40	CMC*	+34/+57	2/10	0.54/4.32	0.13	++	++
46338	14913	20	CMC*	+46/+57	0/10	0.49/4.32	0.11	++	++
46338	14913	10	CMC*	+69/+54	0/5	0.44/4.03	0.11	++	+
34462	19849	0.5	CMC*	+51/+77	0/10	0.68/2.92	0.23	++	++
44593	23191	500	CMC	+54/+55	0/5	3.29/3.37	0.98	−	−
64928	25813	125	PO	+53/+86	0/5	3.50/3.98	0.88	−	−
66352	26927	500	CMC*	+12/+37	1/10	1.34/3.53	0.38	+	−
66349	26928	500	CMC*	+33/+34	0/15	2.48/3.18	0.78	−	−
23909	24464	20	S*	+6/+41	1/15	2.15/3.41	0.63	±	−
409962	27702	8.0	S*	−10/+36	0/10	0.60/3.24	0.19	++	++
409962	27702	4.0	S*	+7/+47	0/10	0.61/2.96	0.21	++	±
409962	27702	2.0	S*	+22/+55	0/10	0.76/3.37	0.23	++	±
409962	27702	1.0	S*	+31/+54	0/10	1.42/3.28	0.43	+	−
527408	27408	1.25	S*	+28/+53	0/10	1.24/3.17	0.39	+	+
21199	20656	15	CMC*	+40/+64	1/10	0.91/2.74	0.33	+	−
26750	12066	500	S*	+47/+71	0/10	1.40/2.78	0.50	+	±
5268	26884	250	CMC	+48/+49	1/5	2.05/2.18	0.97	−	−
60409	26883	250	CMC	+55/+49	0/5	2.59/2.18	1.19	−	−
41269	11088	60	CMC*	+41/+66	1/10	0.97/3.38	0.29	+	±
47774	24591	25	CMC*	+41/+71	0/10	1.10/2.65	0.42	+	±
47774	24591	15	CMC*	+63/+59	2/5	1.73/3.70	0.47	+	−
17016	6699	100	CMC	+6/+54	0/10	0.82/3.83	0.21	++	±
750	5681	5.0	PO	+40/+60	4/20	0.67/3.28	0.20	++	+
750	5681	3.0	PO	+48/+36	1/10	2.64/3.07	0.86	−	−
3052	7505	100	PO	+45/+64	2/5	0.75/3.01	0.25	++	+

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
3052	7505	50	PO	+21/+41	1/20	0.51/3.11	0.16	++	++
524469	24469	1.0	S	−17/+59	2/5	0.48/1.44	0.33	+	±
524469	24469	0.25	S	+59/+56	0/10	1.72/3.86	0.45	+	±
529213	29213	1.0	CMC	+50/+59	0/10	1.22/3.15	0.39	+	±
84641	29102	40	CMC	+8/+46	0/10	0.49/3.58	0.14	++	+
3094	11687	50	PO	+1/+44	2/15	2.43/3.47	0.70	±	−
3094	11687	25	PO	+38/+57	1/5	2.17/2.92	0.74	±	−
408428	14405	125	CMC	+11/+43	2/10	2.22/3.60	0.62	±	−
48821	15128	50	S	+2/+23	2/10	0.69/1.55	0.45	+	−
136059	7503	35	PO	+23/+45	2/10	1.47/1.40	1.05	−	−
—	15749	250	PO	+42/+51	2/15	2.03/2.54	0.80	−	−
49421	4614	1.0	S*	+18/+45	1/15	0.33/2.08	0.15	++	++
9717	3818	1.0	S*	+34/+45	2/15	0.18/2.08	0.09	++	++
26271	20501	25	S*	+4/+62	4/20	0.30/3.02	0.10	++	++
26271	20501	12.5	S*	+10/+73	0/10	0.50/2.95	0.17	++	++
26271	20501	6.25	S*	+60/+73	0/10	0.67/2.95	0.23	++	++
520644	20644	10	CMC*	+40/+64	0/10	0.66/2.90	0.23	++	+
520645	20645	50	CMC*	+40/+52	0/10	0.56/2.92	0.19	++	++
520645	20645	25	CMC*	+44/+69	1/5	0.64/3.52	0.18	++	+
520646	20646	15	CMC*	+24/+83	1/10	0.34/2.70	0.13	++	++
520647	20647	20	CMC*	+29/+90	1/10	0.20/2.48	0.08	++	+
42158	17360	40	S*	−20/+45	2/10	0.49/2.58	0.19	++	+
42158	17360	20	S*	+12/+37	0/5	0.79/2.79	0.28	+	±
—	15385	7.5	S*	−18/+69	1/5	0.37/2.73	0.14	++	+
—	15385	5.0	S*	+11/+50	2/10	0.34/2.92	0.12	++	+
—	15385	2.5	S*	+20/+45	0/5	1.06/2.58	0.41	+	−
26806	22595	10	S	+25/+53	0/10	0.69/3.35	0.21	++	++
—	2732	500	S*	+8/+51	0/25	0.71/3.15	0.23	++	+
—	2732	400	S*	−4/+56	2/5	2.50/4.50	0.56	±	−
—	2732	200	S*	+25/+56	2/5	3.80/4.50	0.84	−	−
9706	1133	0.5	S*	−19/+55	2/5	0.21/2.10	0.10	++	+++
9706	1133	0.25	S*	+4/+45	2/45	0.30/3.41	0.09	++	+++
9706	1133	0.125	S*	+24/+56	5/35	0.28/3.24	0.09	++	++
9706	1133	0.0625	S*	+58/+54	2/10	0.46/3.74	0.12	++	+
9706	1133	0.0313	S*	+47/+54	1/5	1.70/3.46	0.49	+	−
6396	6882	2.0	S*	+28/+56	1/20	0.52/2.72	0.19	++	+++
6396	6882	1.0	S*	+32/+55	1/10	0.57/3.39	0.17	++	++
528988	28988	10	CMC	+23/+58	2/10	0.48/3.32	0.14	++	++
48225	4383	0.5	S*	+7/+49	4/15	0.44/2.51	0.18	++	+
48225	4383	0.25	S*	+37/+40	4/10	0.39/2.40	0.16	++	+
				II. Pyrimidine Analogs					
19893	18143	25	S	+30/+48	1/20	2.00/2.80	0.71	±	−
19893	18143	17.5	S	+50/+40	1/5	2.63/2.28	1.15	−	−
3425	13056	500	CMC	+48/+62	1/5	1.71/2.73	0.63	±	−
529351	29423	50	CMC	+41/+60	0/5	2.57/2.31	1.11	−	−
1589	11770	250	S	+54/+55	2/5	5.00/3.36	1.49	−	−
73376	6959	400	S	+66/+66	0/5	3.61/3.72	0.97	−	−
146604	19273	5.0	S	+63/+61	0/5	2.62/2.63	1.00	−	−
27640	19150	40	S	+51/+53	0/10	2.56/3.22	0.80	−	−
67670	20298	60	CMC	+16/+68	0/5	2.25/3.32	0.68	±	−
9791	5440	150	GA	+35/+45	0/5	3.43/2.85	1.20	−	−
31712	18354	20	S	+51/+72	0/5	2.43/2.48	0.98	−	−
3061	5051	10	CMC	+70/+61	0/10	3.89/2.71	1.44	−	−

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
3062	5266	15	CMC	+18/+43	2/5	2.15/2.92	0.74	±	–
3062	5266	10	CMC	+40/+61	2/10	1.55/2.71	0.57	±	–
—	29511	60	CMC	−1/+48	2/5	3.43/3.80	0.90	–	–
520866	20866	250	CMC	+7/+47	0/5	3.01/3.02	1.00	–	–
—	29217	50	CMC	+36/+46	0/5	1.89/2.46	0.77	–	–
48006	20000	10	S	+23/+36	0/10	1.33/3.22	0.41	–	–
—	6883	2.0	S	+54/+71	0/10	3.24/2.80	1.16	–	–
514427	14427	250	CMC	+38/+47	1/5	2.85/3.02	0.94	–	–
				III. Purines and Analogs					
14666	1387	100	GA	+34/+50	0/5	3.48/3.03	1.15	–	–
3702	1493	125	CMC	+53/+50	0/5	3.58/3.03	1.18	–	–
14664	1494	250	GA	+38/+39	0/5	3.58/3.74	0.96	–	–
110037	17359	50	CMC	+60/+62	0/5	3.36/3.25	1.03	–	–
527612	27612	10	CMC	+46/+62	0/5	3.18/3.25	0.98	–	–
528403	28403	35	A+C	+48/+62	0/10	3.51/3.25	1.08	–	–
—	29830	35	CMC	+39/+51	0/5	2.20/2.50	0.88	–	–
749	1150	100	CMC	+22/+44	0/10	2.55/2.41	1.06	–	–
749	1150	75	CMC	+41/+55	0/20	3.08/2.92	1.05	–	–
756	1149	250	GA	+44/+59	1/10	3.36/3.31	1.02	–	–
—	19994	10	S	+61/+69	1/5	2.74/2.91	0.94	–	–
753	8709	250	S	+15/+43	1/5	2.47/2.97	0.83	–	–
744	6048	150	CMC	+44/+43	0/5	3.05/2.97	1.03	–	–
77640	7347	20	CMC	+40/+50	2/10	3.05/3.71	0.82	–	–
77640	7347	15	CMC	+32/+63	0/5	2.93/3.50	0.84	–	–
—	30002	62.5	CMC	+14/+31	1/5	1.71/1.60	1.07	–	–
513473	13473	100	S	+43/+41	2/10	1.56/2.46	0.63	±	–
25650	14944	100	S	+38/+53	2/5	1.47/2.33	0.63	±	–
526180	26180	60	CMC*	+26/+52	0/15	2.44/3.70	0.66	±	–
526485	26485	60	PO	+6/+48	1/10	1.28/2.90	0.44	+	–
528837	28837	10	A+C	+34/+43	0/5	3.10/3.33	0.93	–	–
755	5357	50	CMC	+18/+57	1/10	0.99/2.62	0.38	+	±
755	5357	30	CMC	+38/+71	0/5	3.51/3.97	0.89	–	–
755	5357	20	CMC	+29/+39	1/10	2.40/3.56	0.67	±	–
528013	28013	250	S	+3/+67	0/10	1.13/2.80	0.40	+	–
38887	20355	10	CMC	+27/+57	0/5	1.48/2.64	0.56	±	–
39084	20354	100	CMC	+21/+57	1/5	1.38/2.64	0.52	±	–
743	1395	60	S	+17/+49	1/25	1.91/2.93	0.65	±	–
752	5459	30	CMC	+38/+51	0/15	3.20/3.46	0.92	–	–
58385	14377	15	CMC	+43/+52	2/5	2.38/2.76	0.86	–	–
58385	14377	10	CMC	+46/+62	0/5	2.80/2.84	0.99	–	–
759	1509	125	S	+58/+63	1/20	3.00/3.17	0.95	–	–
25652	17902	250	CMC	+53/+40	0/5	2.37/2.76	0.86	–	–
25165	18094	100	S	+63/+72	0/5	1.81/2.52	0.72	±	–
25165	18094	50	S	+50/+59	0/5	2.23/1.96	1.14	–	–
4911	12355	100	CMC	+37/+18	1/10	0.78/2.10	0.37	+	–
520950	20950	25	PO	+26/+67	1/10	0.85/2.49	0.34	+	–
29422	18615	2.5	CMC	+50/+62	2/10	2.48/2.36	1.05	–	–
—	4901	200	GA	+45/+27	1/5	1.17/1.55	0.75	±	–
749	1150	200	CMC	0/+50	0/10	1.93/2.44	0.79	–	–
529509	29509	100	CMC	+36/+31	0/5	1.60/1.54	1.04	–	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+20/+57	11/35	2.51/3.38	0.74	±	–

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
742	9505	2.0	S*	+16/+54	3/20	2.23/3.50	0.64	±	–
7365	13835	0.05	S*	+53/+58	2/10	3.09/3.60	0.86	–	–
3063	591	75	CMC	+42/+57	1/10	2.36/2.68	0.88	–	–
—	15894	250	CMC	+42/+52	2/5	3.82/3.24	1.18	–	–
1393	13148	15	CMC	+1/+56	2/5	1.53/2.34	0.65	±	–
1393	13148	10	CMC	+26/+41	0/5	1.67/3.11	0.54	±	–
5197	13640	5.0	CMC	+55/+20	1/5	2.65/3.03	0.87	–	–
—	1833	400	CMC	−16/+50	4/10	1.30/2.81	0.46	+	–
—	1833	200	CMC	+22/+45	0/5	2.98/3.50	0.85	–	–
3073	642	50	S*	+75/+47	1/5	1.69/2.48	0.68	±	–
739	1072	0.25	S*	+1/+46	4/10	1.62/2.84	0.57	±	–
740	1275	0.5	S*	+17/+57	6/20	1.40/2.78	0.50	+	±
740	1275	0.25	S*	+7/+51	4/10	1.50/2.62	0.57	±	–
740	1275	0.125	S*	+29/+51	2/10	2.11/2.62	0.81	–	–
—	24813	3.0	CMC	+46/+59	2/5	3.83/4.09	0.94	–	–
—	1418	500	GA	+75/+64	2/10	5.13/4.06	1.26	–	–
				V. Steroids					
49420E	2795	50	CMC	−8/+42	2/30	1.95/2.80	0.70	±	–
49420E	2795	37.5	CMC	−2/+30	0/5	2.24/2.83	0.79	–	–
49420E	2795	25	CMC	+1/+55	0/5	3.28/3.35	0.98	–	–
10483E	3047	25	CMC	−12/+64	2/10	1.96/4.06	0.48	+	–
12600E	15347	3.0	CMC	+5/+51	1/15	1.33/2.68	0.50	+	–
12600E	15347	1.5	CMC	+8/+59	2/5	1.65/3.12	0.53	±	–
12601E	18062	2.5	CMC	+1/+53	2/10	1.81/3.29	0.55	±	–
9166E	2799	500	CMC	+46/+68	2/10	3.14/3.43	0.92	–	–
9565E	2931	500	CMC	+60/+59	1/5	3.57/3.12	1.14	–	–
9565E	2931	375	CMC	+34/+64	2/15	1.30/2.32	0.56	±	–
9564E	17653	500	CMC	+4/+67	0/5	2.52/2.44	1.03	–	–
3351E	17469	375	CMC	+44/+40	1/5	1.34/2.44	0.55	±	–
10704E	16816	375	CMC	+52/+67	0/5	1.98/2.48	0.80	–	–
12198E	21102	500	CMC	+64/+68	0/5	3.45/3.52	0.98	–	–
50908E	27754	250	CMC	+46/+40	0/5	3.56/3.21	1.11	–	–
—	3092	10	GA	+37/+64	2/5	2.27/3.01	0.75	±	–
20293E	10696	40	CMC	+22/+45	3/15	3.05/3.56	0.86	–	–
20293E	10696	20	CMC	+10/+59	0/5	2.05/2.57	0.80	–	–
20293E	10696	10	CMC	+26/+67	0/5	2.47/2.44	1.01	–	–
23759E	20379	500	CMC	+43/+67	0/10	3.11/3.05	1.02	–	–
				VI. Antibiotics					
402815+	2405	2000	S*	+45/+46	0/5	4.30/4.30	1.00	–	–
14083	4516	500	S	+58/+55	0/5	3.80/3.40	1.12	–	–
3069	2155	500	CMC*	+35/+46	1/15	2.77/3.16	0.88	–	–
13252	1333	50	GA*	+49/+46	0/5	3.70/4.30	0.86	–	–
9169	2859	150	S	+26/+58	0/5	2.80/2.70	1.04	–	–
186	531	10	CMC	+47/+68	2/5	1.82/3.03	0.60	±	–
185	903	1.0	S	+27/+56	4/10	1.18/3.08	0.38	+	–
185	903	0.5	S	+45/+53	2/5	1.77/3.40	0.52	±	–
185	903	0.25	S	+56/+53	0/5	2.81/3.40	0.83	–	–
17257	17442	0.5	S	+47/62	0/5	2.79/3.29	0.85	–	–
—	2163	12.5	CMC	+58/+56	0/5	1.96/3.28	0.60	±	–
3067	2662	15	CMC	+8/+61	1/10	2.81/2.71	1.04	–	–
—	2935	0.5	S	+2/+66	2/5	2.75/3.03	0.91	–	–
400978	4996	0.5	S	0/+71	2/5	1.63/2.81	0.58	±	–

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
9168	6258	5.0	CMC	+13/+55	5/15	1.00/3.14	0.32	+	–
—	862	0.02	S	+58/+50	0/5	4.09/3.71	1.10	–	–
25792	12878	0.02	CMC	+18/+59	4/10	2.93/3.28	0.89	–	–
18268	11822	0.05	A+S	+24/+53	1/5	2.45/3.73	0.66	±	–
18268	11822	0.025	A+S	+5/+61	4/10	1.55/2.58	0.60	±	–
3053	14095	0.05	A+S	+34/+85	2/5	2.87/3.19	0.90	–	–
3053	14095	0.025	A+S	+38/+54	1/15	3.44/3.43	1.00	–	–
48077	20403	0.1	A+S	+42/+64	1/5	2.16/2.71	0.80	–	–
—	12501	0.02	CMC	+46/+57	1/5	3.36/2.68	1.25	–	–
14347	12772	250	S*	+48/+63	1/5	3.98/3.18	1.25	–	–
26980	19256	1.0	S	+5/+63	2/15	0.54/3.16	0.17	++	++
26980	19256	0.5	S	+7/+54	1/10	0.82/2.98	0.28	+	±
26980	19256	0.25	S	+42/+54	0/10	1.61/3.46	0.47	+	–
56410	20779	2.0	S	+31/+32	0/5	2.44/3.29	0.74	±	–
—	28008	2.0	S	−9/+43	2/10	0.22/3.29	0.07	++	++
—	28009	2.5	A+S	−16/+43	2/5	0.25/3.29	0.08	++	+++
—	28009	1.25	A+S	−7/+63	0/10	0.12/3.00	0.04	++	+++
—	28010	2.5	S	−14/+43	2/10	0.31/3.29	0.09	++	++
—	28145	2.5	A+S	+37/+58	0/10	3.66/3.36	1.09	–	–
—	28146	2.5	A+S	−26/+53	4/15	0.63/3.46	0.18	++	++
—	28242	5.0	A+S	+5/+50	0/10	0.56/3.54	0.16	++	+
524678	24678	1.0	S	+36/+63	2/15	1.79/3.04	0.59	±	–
3055	12414	50	S	+26/+63	3/10	1.95/3.42	0.57	±	–
64393	14155	125	S	+46/+58	2/5	3.40/2.62	1.30	–	–
105388	17277	2.0	A+S	+46/+64	0/5	2.73/2.93	0.93	–	–
105388	17277	1.0	A+S	+46/+50	1/5	2.85/2.92	0.98	–	–
—	19439	500	S	+42/+32	1/5	2.55/2.68	0.95	–	–
58514	20863	0.05	S*	+47/+64	0/10	2.45/2.85	0.86	–	–
58514	20863	0.025	S*	+19/+39	0/5	2.29/2.96	0.77	–	–
58856	25707	1.25	A+W	+52/+58	0/5	2.96/2.62	1.13	–	–
58856	25707	0.625	A+W	+44/+52	1/5	1.88/1.58	1.19	–	–
526417	26417	0.025	A+S	+33/+62	3/15	2.28/3.06	0.75	±	–
526094	26094	0.01	A+S	+22/+45	2/5	3.15/3.46	0.91	–	–
526094	26094	0.005	A+S	+19/+55	1/5	2.66/1.89	1.41	–	–
525822	25822	0.005	A+S	+53/+58	0/5	2.93/2.62	1.12	–	–
525822	25822	0.00258	A+S	+43/+67	0/5	1.81/3.22	0.56	±	–
24559	20047	0.3	S	+58/+65	0/5	257/2.71	0.95	–	–
83340	28487	5.0	S	+2/+56	1/20	2.40/3.81	0.63	±	–
52947	27773	1.0	S*	+52/+59	0/5	3.45/3.80	0.91	–	–
59729	28430	0.5	S	+1/+56	0/5	1.81/3.48	0.52	±	–
65423	9749	5.0	S	+65/+19	4/10	2.37/3.03	0.78	–	–
—	12780	0.1	CMC	+65/+62	1/5	3.96/3.84	1.03	–	–
76029	13328	2500	S	+30/+61	0/5	3.59/3.78	0.95	–	–
39147	20250	0.15	S	+43/+55	2/10	1.98/2.49	0.80	–	–
45383	20556	0.1	A+S	+17/+69	3/15	1.65/3.31	0.50	+	–
45383	20556	0.05	A+S	+10/+49	0/5	2.13/1.84	1.15	–	–
53104	21568	500	CMC	+28/+62	0/10	1.20/3.56	0.34	+	–
521778	21778	2000	S	+56/+63	0/10	2.34/3.43	0.68	±	–
31083	21721	1000	S	+58/+68	0/5	2.53/3.52	0.72	±	–
31083	21721	250	S	+47/+62	0/10	3.00/3.37	0.89	–	–
526368	26368	1.0	CMC	+39/+62	0/10	3.01/3.06	0.98	–	–
51812	24907	40	CMC*	+53/+69	0/5	3.38/3.52	0.96	–	–
526598	26598	0.25	CMC	+63/+55	1/5	4.20/3.49	1.20	–	–
56408	26996	0.5	S	+25/+86	1/5	3.31/3.98	0.83	–	–

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
56410	25021	0.2	S	+37/+83	1/10	0.65/1.63	0.40	+	−
56410	25021	0.1	S	+12/+59	0/5	1.93/3.29	0.59	±	−
—	30133	2.5	CMC	+30/+51	0/5	1.34/2.35	0.57	±	−
3067	2662	15	CMC	+8/+61	1/10	2.81/2.71	1.04	−	−
—	18355	0.05	S*	+80/+77	0/5	2.53/2.90	0.87	−	−
				VII. Quinolines					
3396	2397	75	PG	+39/+50	2/5	2.40/2.41	1.00	−	−
4141	11874	50	CMC	+36/+53	1/5	1.77/1.84	0.96	−	−
346	9408	50	CMC	+63/+54	2/5	2.01/2.26	0.89	−	−
732	14136	50	CMC	+59/+67	0/5	1.97/2.26	0.87	−	−
528997	28997	12.5	CMC	+51/+63	1/5	3.51/4.13	0.85	−	−
528995	28995	25	CMC	+50/+63	0/5	3.24/4.13	0.78	−	−
529105	29105	15	CMC	+23/+49	0/5	2.63/3.22	0.82	−	−
528996	28996	2.5	CMC	+44/+63	0/5	3.69/4.31	0.86	−	−
529103	29103	2.0	CMC	+36/+44	0/5	3.69/3.15	1.17	−	−
529103	29103	1.0	CMC	+45/+43	0/5	2.52/3.26	0.77	−	−
19645	16292	2.5	CMC	+48/+67	1/5	1.34/2.26	0.59	±	−
—	16293	4.0	CMC	+28/+67	0/10	1.02/2.26	0.45	+	−
529104	29104	25	CMC	+30/+49	0/5	3.30/3.22	1.02	−	−
				VIII. Miscellaneous Compounds					
757	280	0.5	S	+15/+65	0/10	3.11/3.35	0.93	−	−
757	280	0.25	S	+20/+31	1/5	2.84/2.78	1.02	−	−
9170	15025	20	S	+24+61	2/10	2.71/4.06	0.67	±	−
9170	15025	10	S	+67/+61	0/5	2.38/2.31	1.03	−	−
3096	11626	1.5	S	+54/+54	1/5	2.37/3.83	0.62	±	−
—	19121	10	CMC	+31/+71	0/5	2.80/2.74	1.02	−	−
—	21509	250	CMC	+62/+66	0/5	3.06/3.05	1.00	−	−
46096	3615	62.5	BC	+47/+58	0/5	3.00/2.70	1.11	−	−
13875	1905	250	CMC*	+32/+77	4/10	0.76/2.92	0.26	+	+
13875	1905	125	CMC*	+38/+50	1/15	1.01/2.34	0.43	+	−
13875	1905	75	CMC*	+24/+41	0/5	2.01/2.84	0.71	±	−
13875	1905	37.5	CMC*	+21/+41	0/5	2.75/2.84	0.97	−	−
525816	25816	50	S	+58/+52	0/5	2.75/3.10	0.89	−	−
525661	25661	2.5	S*	+38/+59	0/5	1.21/1.44	0.84	−	−
4	3844	200	CMC	+35/+52	0/5	2.69/2.92	0.92	−	−
4	3844	75	CMC	+56/+71	1/5	3.88/2.81	1.38	−	−
401593	14071	25	S	+63/+63	0/5	3.53/3.18	1.11	−	−
4794	1356	5.0	S	+54/+45	0/5	3.53/2.85	1.24	−	−
14574	1471	50	S	+53/+71	0/5	3.63/3.97	0.91	−	−
—	1866	10	CMC	+35/+45	0/5	2.95/2.85	1.04	−	−
11926	26153	1.0	S	+20/+45	1/5	2.64/3.46	0.76	−	−
67574	26327	0.125	S	+18/+44	0/10	2.09/2.32	0.90	−	−
12865	11258	125	CMC	+63/+71	1/5	4.94/3.37	1.47	−	−
3089	14950	15	CMC	+56/+58	0/5	2.26/3.00	0.75	±	−
33963	18766	30	CMC	+31/+53	1/5	1.37/2.33	0.59	±	−
34162	16844	20	S*	+39/+50	2/5	2.12/2.41	0.88	−	−
34162	16844	10	S*	+57/+58	2/10	2.71/3.08	0.88	−	−
4730	14406	37.5	S	+34/+54	2/10	1.10/2.77	0.40	+	±
—	13808	250	CMC	+32/+59	1/5	1.56/1.96	0.80	−	−
—	1577	100	PG	+44/+44	0/5	3.15/3.50	0.90	−	−
59354	25627	250	CMC	+33/+59	2/10	1.88/2.53	0.74	±	−
5354	1147	200	S*	−17/+58	0/5	2.49/3.23	0.77	−	−
5354	1147	100	S*	+38/+59	1/5	1.69/1.96	0.86	−	−

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
—	7396	0.1	PG	+59/+58	0/5	3.40/3.62	0.94	−	−
8538	19801	15	CMC	+56/+72	2/5	2.60/3.00	0.87	−	−
—	20547	50	CMC	+34/+36	0/5	2.80/3.22	0.87	−	−
525602	25602	6.25	S*	−54/+66	3/15	2.67/2.93	0.91	−	−
522679	22679	500	CMC	+53/+62	0/5	3.30/3.21	1.03	−	−
21666	25825	75	CMC	+50/+59	0/5	4.10/3.29	1.25	−	−
527516	27516	25	CMC	+9/+59	1/5	4.08/3.84	1.06	−	−
66248	26071	100	CMC*	+3/+52	2/5	1.12/1.58	0.71	±	−
525442	25442	125	CMC	+49/+39	0/5	3.32/3.14	1.06	−	−
53582	25513	62.5	CMC*	+16/+66	0/10	1.15/4.26	0.27	+	−
53582	25513	30	CMC*	+41/+61	0/10	1.11/3.34	0.33	+	±
49403	25512	125	CMC	+60/+59	2/5	1.45/3.86	0.38	+	−
49403	25512	62.5	CMC	+51/+67	0/10	1.46/3.22	0.45	+	±
—	1380	125	CMC	+54/+67	0/5	1.80/2.48	0.73	±	−
405	23102	250	CMC	+46/+54	1/5	3.52/3.54	0.99	−	−
—	16683	125	CMC	+33/+56	2/10	1.25/2.37	0.53	±	−
23306	26081	60	CMC*	+71/+74	0/10	2.31/3.79	0.61	±	−
2100	384	50	GA	+45/+35	0/10	1.87/1.74	1.07	−	−
3065	10826	250	CMC	−5/+67	2/5	3.13/3.78	0.83	−	−
—	13459	50	CMC	+68/+47	0/5	2.50/2.48	1.01	−	−
522558	22558	500	CMC	+55/+68	0/5	3.29/3.32	0.99	−	−
25647	2401	17.5	CMC	+58/+71	2/5	2.66/2.78	0.96	−	−
34540	24297	150	S	+16/+65	0/5	3.11/3.12	1.00	−	−
—	18999	25	CMC	+70/+70	0/5	2.78/3.11	0.89	−	−
—	22388	200	CMC	+35/+73	0/5	3.29/2.95	1.12	−	−
36539	24298	160	CMC	+25/+65	0/5	3.22/3.12	1.03	−	−
45409	24299	80	CMC	+39/+63	2/5	3.23/2.61	1.23	−	−
—	28239	50	A+S	−14/+38	2/5	0.50/3.08	0.16	++	++
—	28239	25	A+S	−10/+46	0/10	0.32/1.97	0.16	++	++
—	28265	50	A+S	+32/+38	0/5	3.68/3.08	1.19	−	−
527517	27517	10	CMC	+40/+59	2/5	3.73/3.94	0.95	−	−
527517	27517	5.0	CMC	+29/+46	0/5	3.71/3.85	0.97	−	−
21206	15928	1.0	CMC	−15/+72	2/5	2.78/2.52	1.10	−	−
522600	22600	30	CMC	+15/+39	1/5	2.84/3.14	0.90	−	−
31659	19453	0.5	S	−54/+72	0/5	2.68/3.00	0.89	−	−
3071	12356	25	CMC	+28/+69	4/10	3.65/3.35	1.09	−	−
—	12356	10	CMC	+46/+58	1/10	3.82/3.49	1.09	−	−
523485	23485	7.5	CMC	+51/+63	0/5	2.36/3.04	0.78	−	−
523484	23484	15	CMC	−40/+64	1/15	2.94/3.49	0.84	−	−
523486	23486	4.0	CMC	+20/+63	2/10	1.03/2.68	0.38	+	−
758	1812	1,500	S	+51/+47	1/10	3.56/3.47	1.03	−	−
758	1812	750	S	−39/+52	1/10	3.86/3.28	1.18	−	−
17559	22575	250	CMC	+35/+54	0/5	3.46/3.30	1.05	−	−
—	19918	200	S	+65/−64	0/5	2.70/2.71	1.00	−	−
—	22841	500	S*	+55/+67	0/5	3.27/3.20	1.02	−	−
—	16395	100	S*	+67/+54	0/5	2.44/2.26	1.08	−	−
8102	8028	5,000	S	−59/+32	0/5	1.58/2.38	0.66	±	−
15193	7305	300	S	+57/+65	1/5	3.55/3.03	1.17	−	−
24854	20895	1,000	S	+71/+63	1/5	3.50/2.61	1.34	−	−
54186	24580	25	S*	+78/−63	1/5	3.15/2.61	1.21	−	−
524784	24784	2.0	S*	+66/+66	0/5	2.99/2.92	1.02	−	−
521828	21828	250	CMC	+52/+58	0/5	3.43/2.62	1.31	−	−
—	2[illegible]197	250	S	+13/−57	0/5	2.59/2.84	0.91	−	−
—	8125	1,000	S	+40/+41	0/5	3.66/3.23	1.13	−	−
7786	13943	100	S	+17/+50	1/5	1.26/2.41	0.52	±	−

TABLE 3.—Effect of compounds on Walker carcinosarcoma 256—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
751	5393	500	CMC	+25/+57	0/10	2.85/2.68	1.06	–	–
109229	30000	10,000 IU	S	+19/+33	0/5	0.15/1.99	0.08	++	++
109229	30000	5,000 IU	S	+31/+54	0/5	0.26/2.51	0.10	++	++
109229	30000	167 IU	S	+48/+56	0/5	1.90/2.26	0.84	–	–
35843	24759	125	S	+23/+59	1/5	3.72/3.29	1.13	–	–
35847	24760	8.0	CMC	+9/+58	2/5	2.85/2.62	1.09	–	–
38280	24761	16	S	+20/+58	1/5	3.03/2.62	1.16	–	–
527179	27179	1,000	A+C*	+21/+53	0/10	2.44/3.40	0.72	±	–
748	7078	200	S	+43/+59	0/5	3.28/3.52	0.93	–	–
748	7078	125	S	+38/+53	0/10	2.71/2.92	0.93	–	–
3051	8328	250	S	+21/+62	5/20	1.91/3.54	0.54	±	–
3051	8328	200	S	+7/+56	4/10	2.07/3.66	0.57	±	–
—	3828	125	S	+16/+56	3/10	2.46/3.68	0.67	±	–
—	3828	62.5	S	+42/+58	1/5	3.34/3.81	0.88	–	–
747	6479	750	PG	+41/−44	3/10	1.78/3.01	0.59	±	–
3054	3501	500	S	+36/+60	1/10	1.85/2.16	0.86	–	–
32065	22591	200	CMC	+31/+57	0/5	3.14/2.84	1.11	–	–
32065	22591	100	CMC	+44/+64	0/10	2.67/3.05	0.88	–	–
3095	2917	75	S	+9/+60	1/10	2.09/2.16	0.97	–	–
10924	156	250	CMC	+32/+63	2/5	2.61/2.60	1.00	–	–
746	129	1,000	S	0/+46	1/5	2.90/4.30	0.67	±	–
746	129	500	S	+26/+54	1/25	2.00/3.52	0.57	±	–
6170	50	125	PO	+73/+62	0/5	2.47/2.73	0.90	–	–
3769	610	9.0	S	+54/+43	0/5	3.66/2.92	1.25	–	–
3769	610	6.0	S	+59/+63	1/5	3.15/3.29	0.96	–	–
—	7397	10	S	+35/+58	1/5	3.25/3.40	0.96	–	–
25649	8856	100	CMC	+73/+63	2/5	3.55/2.61	1.36	–	–
25649	8856	50	CMC	+45/+71	0/5	2.28/2.78	0.82	–	–
27223	16767	150	S*	+72/+77	0/5	3.48/3.27	1.06	–	–
30418	16850	500	CMC	+54/+40	2/5	3.18/2.28	1.39	–	–
139	27091	30	CMC	+27/+46	2/10	3.82/4,63	0.83	–	–
—	20890	10	S*	+42/+62	2/5	2.56/3.29	0.78	–	–
—	8800	0.1	S*	+45/+63	2/5	1.95/2.80	0.70	±	–
526741	26741	31.25	PO	+43/+55	0/5	3.53/3.37	1.05	–	–
526739	26739	500	PO	+48/+55	0/5	2.61/3.37	0.77	–	–
—	26744	15	PO	+47/+55	0/5	3.43/3.37	1.02	–	–
25648	5326	200	CMC	+52/+71	1/5	2.82/2.78	1.01	–	–
523316	23316	20	CMC	+70/+63	0/5	3.37/3.07	1.10	–	–
523313	23313	5.0	S	+62/+50	2/5	3.63/3.72	0.98	–	–
523314	23314	8.0	CMC	+52/+63	0/5	2.94/3.07	0.96	–	–
12693	23315	20	CMC	+72/+50	2/5	3.85/3.72	1.03	–	–
—	20547	50	CMC	+34/+36	0/5	2.80/3.22	0.87	–	–
3060	420	8.0	S	+32/+59	1/10	3.63/3.31	1.10	–	–
—	3589	300	S	+46/+46	2/10	1.59/2.00	0.80	–	–
—	29831	20	S	+11/+50	0/5	1.40/1.63	0.86	–	–
—	29857	250	S	+41/+46	0/5	2.84/2.28	1.25	–	–
44690	1039	7.5	CMC	+39/+62	2/5	2.88/3.21	0.90	–	–
140865	19272	100	CMC	+61/+54	2/20	2.73/3.01	0.91	–	–
86016	9980	10	S	+48/+82	0/5	3.05/2.75	1.11	–	–
9369	20035	10	CMC	+48/+63	0/5	2.32/2.44	0.95	–	–
80087	30053	200	PO	+32/+43	0/5	1.92/2.10	0.91	–	–
3070	2800	80	CMC	+16/+51	0/5	3.22/4.17	0.77	–	–
3070	2800	40	CMC	+16/+50	1/5	2.79/4.17	0.67	±	–
3070	2800	10	CMC	+16/+55	1/20	2.42/2.59	0.93	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 4.—Effect of compounds on Jensen sarcoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				1. Alkylating Agents					
762	101	0.25	S*	+20/+45	0/20	0.45/4.07	0.11	++	++
762	101	0.125	S*	+47/+53	0/5	2.39/4.08	0.59	±	–
762	101	0.0625	S*	+52/+53	0/5	3.54/4.08	0.87	–	–
10107	598	1.5	S*	−20/+31	1/10	0.0/3.78	0.0	+++	+++
10107	598	0.75	S*	+5/+38	1/10	0.0/4.30	0.0	+++	+++
10107	598	0.5	S*	+17/+32	0/10	0.0/3.41	0.0	+++	+++
10107	598	0.25	S*	+29/+32	0/10	2.12/3.41	0.62	±	–
9506	1424	5.0	PO	−20/+39	1/10	0.31/1.62	0.19	++	+++
8806	15673	1.0	S*	+45/+50	0/15	0.05/3.84	0.01	++	+++
14210	21739	2.0	PO	+22/+52	0/15	0.0/2.44	0.0	+++	+++
—	20598	1.0	S*	+32/+53	0/10	0.0/3.69	0.0	+++	+++
—	20597	1.0	S*	+56/+52	0/10	0.0/3.60	0.0	+++	+++
525691	25691	12.5	CMC	+29/+46	0/10	0.27/3.30	0.08	++	+++
526407	26407	25	CMC	+39/+55	0/10	0.0/4.17	0.0	+++	+++
526407	26407	12.5	CMC	+39/+47	0/5	0.40/2.29	0.17	++	+++
525823	25823	100	CMC*	−11/+53	0/5	0.0/1.06	0.0	+++	+++
525823	25823	50	CMC*	+20/+44	0/10	0.0/4.20	0.0	+++	+++
526622	26622	125	CMC*	+5/+54	0/15	0.02/3.28	0.01	++	+++
525022	25022	100	CMC*	+6/+38	1/15	0.05/3.00	0.02	++	+++
525022	25022	50	CMC*	+19/+44	0/5	0.0/3.49	0.0	+++	+++
525022	25022	25	CMC*	+40/+44	0/5	0.39/3.49	0.11	++	+
526406	26406	25	CMC*	+21/+50	0/10	0.34/3.59	0.09	++	++
527453	27453	50	CMC*	+9/+42	2/10	0.10/2.39	0.04	++	+++
62403	27456	2.0	CMC*	+12/+39	0/5	0.0/3.51	0.0	+++	+++
62403	27456	1.0	CMC*	+12/+42	1/10	0.06/3.41	0.02	++	++
62403	27456	0.5	CMC*	+32/+37	2/10	2.15/3.27	0.66	±	–
23909	24464	20	S*	+21/+58	0/10	3.50/3.19	1.10	–	–
409962	27702	8.0	S*	+5/+39	0/10	0.0/3.13	0.0	+++	+++
409962	27702	4.0	S*	+11/+43	0/10	0.0/3.63	0.0	+++	+++
409962	27702	2.0	S*	+34/+53	0/10	0.16/3.31	0.05	++	++
409962	27702	1.0	S*	+51/+65	0/10	4.02/4.42	0.91	–	–
527408	27408	1.25	S*	+27/+57	2/10	0.0/2.48	0.0	+++	+++
21199	20656	15	CMC*	+23/+71	0/10	0.95/3.80	0.25	++	+
26750	12066	500	S	+37/+53	2/5	4.05/4.91	0.82	–	–
41269	11088	60	CMC*	+36/+63	1/10	0.06/4.11	0.01	++	+++
47774	24591	15	CMC*	+43/+45	3/15	0.46/2.65	0.17	++	++
74437	13595	30	CMC*	+31/+51	0/10	0.11/1.07	0.10	++	+++
17016	6699	100	CMC	+6/+48	3/20	0.23/4.35	0.05	++	+
750	5681	5.0	PO	+27/+45	4/15	0.72/2.82	0.26	+	±
3052	7505	50	PO	+34/+52	1/25	0.0/2.69	0.0	+++	+++
524469	24469	1.0	S	+19/+42	3/10	0.15/1.60	0.09	++	++
524469	24469	0.25	S	+39/+41	0/10	1.02/2.06	0.50	+	±
529213	29213	1.0	CMC	+25/+56	0/10	1.69/3.15	0.54	±	–
84641	29102	40	CMC	+9/+53	9/10	0.09/3.14	0.03	++	++
3094	11687	50	PO	+19/+55	0/10	2.72/3.44	0.79	–	–
408428	14405	250	CMC	+5/+64	0/5	2.50/4.09	0.61	±	–
408428	14405	125	CMC	+10/+58	1/5	1.75/3.43	0.51	±	–
48821	15128	100	S	−4/+60	0/5	2.77/4.04	0.69	±	–
3094	11687	35	PO	+56/+60	1/5	4.44/4.04	1.10	–	–
—	15749	250	PO	+48/+61	1/10	1.61/3.29	0.49	+	–
49421	4614	1.0	S*	+26/+43	4/30	0.56/4.04	0.14	++	+++
9717	3818	1.0	S	+40/+57	0/20	0.0/4.02	0.0	+++	+++
26271	20501	50	S*	−9/+46	4/15	0.0/3.44	0.0	+++	+++

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
26271	20501	25	S*	−1/+49	0/10	0.0/2.53	0.0	+++	+++
26271	20501	12.5	S*	+31/+49	0/20	0.15/2.73	0.05	++	+++
26271	20501	6.25	S*	+25/+49	0/10	0.0/2.90	0.0	+++	+++
26271	20501	3.13	S*	+30/+51	0/5	0.50/3.05	0.16	++	+
520644	20644	25	CMC*	−1/+49	2/10	0.0/3.55	0.0	+++	+++
520645	20645	50	CMC*	+23/+60	0/10	0.0/3.71	0.0	+++	+++
520646	20646	30	CMC*	+14/+70	0/5	0.0/4.82	0.0	+++	+++
520646	20646	15	CMC*	+21/+63	0/10	0.0/3.91	0.0	+++	+++
520647	20647	40	CMC*	+48/+70	0/10	0.0/4.82	0.0	+++	+++
520647	20647	20	CMC*	+26/+71	0/5	0.17/4.25	0.04	++	+
42158	17360	40	S*	+17/+49	2/10	0.0/3.95	0.0	+++	+++
42158	17360	20	S*	+39/+80	0/5	0.0/4.39	0.0	+++	+++
9706	1133	0.25	S*	−12/+45	2/15	0.40/2.94	0.14	++	+++
9706	1133	0.125	S*	+38/+48	2/15	0.0/4.02	0.0	+++	+++
9706	1133	0.0625	S*	+29/+53	0/10	0.0/4.08	0.0	+++	+++
9706	1133	0.0313	S*	+46/+53	0/5	0.35/4.08	0.09	++	++
6396	6882	4.0	S*	−15/+49	4/10	0.0/3.71	0.0	+++	+++
6396	6882	2.0	S*	+9/+46	0/10	0.0/4.09	0.0	+++	+++
6396	6882	1.0	S*	+19/+48	3/20	0.0/3.05	0.0	+++	+++
6396	6882	0.5	S*	+51/+51	0/10	0.0/4.05	0.0	+++	+++
6396	6882	0.25	S*	+32/+45	0/20	1.11/4.28	0.26	+	+
6396	6882	0.10	S*	+50/+40	1/10	3.84/4.09	0.94	−	−
—	15385	7.5	S*	−8/+56	1/5	0.19/3.15	0.06	++	+++
—	15385	5.0	S*	+23/+49	0/10	0.05/4.32	0.01	++	++
528988	28988	10	CMC	+7/+46	1/10	0.0/3.11	0.0	+++	+++
528988	28988	5.0	CMC	+26/+54	0/10	0.0/3.00	0.0	+++	+++
64928	25813	125	PO	+25/+45	1/10	1.31/2.49	0.53	±	−
				II. Pyrimidine Analogs					
19893	18143	25	S	+41/+39	0/5	2.64/3.17	0.83	−	−
19893	18143	17.5	S	+49/+54	0/5	4.02/4.19	0.96	−	−
3425	13056	500	CMC	+34/+45	2/5	2.76/1.98	1.39	−	−
514427	14427	250	CMC	+53/+60	0/5	3.98/4.41	0.90	−	−
529351	29423	50	CMC	+40/+47	0/5	2.56/2.49	1.03	−	−
1589	11770	250	S	+21/+21	0/5	3.43/2.89	1.19	−	−
146604	19273	5.0	S	+47/+41	0/10	3.86/4.32	0.89	−	−
27640	19150	40	S	+47/+48	0/10	1.58/3.57	0.44	+	−
3062	5266	5.0	CMC	+44/+44	0/5	3.48/2.56	1.36	−	−
—	29511	60	CMC	+36/+59	1/5	4.58/4.62	0.99	−	−
—	29217	50	CMC	+50/+46	1/5	3.19/3.66	0.87	−	−
48006	20000	10	S	+34/+52	0/5	2.50/2.81	0.89	−	−
—	6883	2.0	S	+40/+36	0/5	3.94/3.00	1.31	−	−
514427	14427	250	CMC	+53/+60	0/5	3.98/4.41	0.90	−	−
				III. Purines and Analogs					
14666	1387	100	GA	+57/+56	0/5	3.15/2.61	1.21	−	−
3702	1493	125	CMC	+56/+56	0/5	2.17/2.61	0.83	−	−
14664	1494	250	GA	+40/+57	1/5	3.10/4.15	0.75	±	−
110037	17359	50	CMC	+65/+63	0/5	4.29/3.81	1.13	−	−
527612	27612	10	CMC	+45/+56	1/5	4.31/4.17	1.03	−	−
528403	28403	35	A+C	+52/+56	1/5	4.05/4.17	0.97	−	−
749	1150	150	CMC	+25/+37	1/5	3.89/3.21	1.21	−	−
—	19994	10	S	+63/+69	0/5	4.25/2.93	1.45	−	−
753	8709	250	S	−11/+28	1/5	2.91/3.48	0.84	−	−
744	6048	150	CMC	+53/+53	0/5	3.43/3.10	1.11	−	−

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
77640	7347	25	CMC	+27/+45	4/10	2.05/3.19	0.64	±	–
77640	7347	20	CMC	+21/+61	2/10	2.32/3.62	0.64	±	–
514473	13473	150	S	+71/+60	1/5	4.49/4.04	1.11	–	–
514473	13473	100	S	+49/+51	1/5	3.84/3.28	1.17	–	–
25650	14944	100	S	+65/+58	2/5	3.55/3.23	1.10	–	–
526180	26180	60	CMC*	+34/+47	0/5	3.48/3.34	1.04	–	–
526485	26485	60	PO	+22/+46	2/10	1.53/3.74	0.41	+	–
528837	28837	10	A+C	+33/+46	0/5	2.55/3.66	0.70	±	–
755	5357	30	CMC	+36/+56	2/35	2.71/3.27	0.83	–	–
755	5357	20	CMC	+27/+48	0/15	2.77/2.80	0.99	–	–
38887	20355	10	CMC	+36/+80	1/10	1.30/3.33	0.39	+	±
39084	20354	100	CMC	+25/+80	1/5	2.14/3.33	0.64	±	–
752	5459	3.0	CMC	+27/+35	0/10	2.74/2.80	0.98	–	–
58385	14377	10	CMC	+59/+58	0/5	3.88/2.95	1.32	–	–
759	1509	125	S	+49/+56	1/5	3.41/3.15	1.08	–	–
25652	17902	250	CMC	+35/+50	0/5	2.95/3.49	0.84	–	–
3057	1054	50	CMC	+52/+25	0/5	4.85/4.37	1.11	–	–
25165	18094	100	S	+57/+58	0/5	2.74/2.95	0.93	–	–
4911	12355	100	CMC	+15/+72	0/5	2.78/3.92	0.71	±	–
520950	20950	50	PO	+39/+25	2/5	3.01/3.73	0.81	–	–
29422	18615	2.5	CMC	+31/+58	0/5	4.64/3.61	1.29	–	–
56408	26996	0.5	S	+36/+54	0/15	2.40/3.62	0.66	±	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+25/+42	1/15	3.44/3.39	1.01	–	–
7365	13835	0.1	S*	+44/+64	0/5	3.44/4.09	0.84	–	–
7365	13835	0.05	S*	+52/+47	0/10	3.53/3.29	1.09	–	–
1393	13148	15	CMC	−4/+22	1/5	3.76/2.92	1.29	–	–
1393	13148	10	CMC	+44/+73	0/5	2.64/3.27	0.81	–	–
5197	13640	5.0	CMC	+53/+44	2/10	1.09/2.56	0.43	+	–
—	1833	100	CMC	+27/+56	0/5	2.04/2.67	0.76	–	–
3073	642	50	S*	+66/+43	0/10	4.07/3.64	1.12	–	–
3073	642	37.5	S*	+45/+37	0/5	3.37/3.21	1.05	–	–
739	1072	0.25	S*	+24/+22	4/15	0.0/2.61	0.0	+++	+++
740	1275	1.5	S*	+4/+53	1/10	0.04/4.15	0.01	++	++
740	1275	0.75	S*	+31/+55	1/15	0.18/3.60	0.05	++	++
740	1275	0.375	S*	+50/+53	0/10	4.84/4.15	1.17	–	–
—	24813	3.0	CMC	+43/+46	1/5	4.81/4.32	1.11	–	–
—	24815	1.5	CMC	+55/+46	1/5	5.34/4.32	1.24	–	–
—	28757	12.5	A+C	+75/+72	2/5	4.50/4.21	1.07	–	–
				V. Steroids					
49420E	2795	37.5	CMC	+3/+37	0/10	2.54/3.29	0.77	–	–
10483E	3047	37.5	CMC	+19/+53	0/10	2.74/2.86	0.96	–	–
12600E	15347	3.0	CMC	+18/+59	1/10	4.00/3.22	1.24	–	–
12600E	15347	1.5	CMC	+40/+61	0/5	3.97/2.77	1.43	–	–
12601E	18062	25	CMC	−15/+57	4/10	2.48/3.52	0.70	±	–
12601E	18062	6.25	CMC	+12/+58	2/10	3.52/3.48	1.01	–	–
9166E	2799	500	CMC	+47/+54	1/15	3.30/3.32	0.99	–	–
9565E	2931	37.5	CMC	+21/+40	0/5	3.92/2.88	1.36	–	–
9564E	17653	500	CMC	+47/+48	0/5	4.33/4.80	0.90	–	–
3351E	17469	375	CMC	+24/+62	0/5	1.23/2.64	0.47	+	–
10704E	16816	375	CMC	+65/+51	0/5	4.67/3.74	1.25	–	–
12198E	21102	500	CMC	+68/+47	0/5	4.37/3.67	1.19	–	–
20293E	10696	40	CMC	+20/+54	3/25	3.21/3.90	0.82	–	–

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
20293E	10696	20	CMC	+36/+39	1/5	5.02/4.13	1.22	−	−
20293E	10696	10	CMC	+34/+62	0/5	3.68/4.80	0.77	−	−
23759E	20379	500	CMC	+56/+54	0/5	2.90/2.38	1.22	−	−
				VI. Antibiotics					
402815+	2405	2,000	S*	+35/+28	0/5	4.07/3.48	1.17	−	−
14083	4516	500	S	+50/+28	1/5	3.80/3.61	1.05	−	−
3069	2155	500	CMC*	+26/+36	0/10	2.90/3.62	0.80	−	−
9169	2859	150	S	+38/+26	0/5	4.31/4.13	1.04	−	−
186	531	20	CMC	+25/+68	1/5	3.83/4.02	0.95	−	−
186	531	10	CMC	+60/+78	0/5	4.30/4.42	0.97	−	−
185	903	1.0	S	+17/+55	4/25	2.15/3.68	0.58	±	−
185	903	0.5	S	+43/+54	0/5	3.53/3.75	0.94	−	−
17257	17442	1.25	S	+20/+68	2/10	1.80/4.02	0.45	+	±
17257	17442	1.0	S	+32/+71	1/5	3.06/3.80	0.81	−	−
—	2163	12.5	CMC	+12/+21	1/5	3.91/2.89	1.35	−	−
3067	2662	15	CMC	−11/+42	0/5	2.76/3.81	0.72	±	−
400978	4996	0.5	S	+28/+43	4/10	2.67/3.28	0.81	−	−
9168	6258	15	CMC	−26/+40	4/10	0.64/2.86	0.22	++	±
9168	6258	10	CMC	−1/+53	3/15	1.20/3.51	0.34	+	±
9168	6258	5.0	CMC	+35/+46	2/20	2.04/3.18	0.64	±	−
58368	13617	50	CMC*	+23/+47	0/10	1.79/1.33	1.35	−	−
18268	11822	0.025	A+S	+39/+51	0/15	2.03/2.83	0.72	±	−
3053	14095	0.05	A+S	+24/+30	0/15	1.96/2.43	0.81	−	−
3053	14095	0.025	A+S	+40/+34	1/20	2.26/2.73	0.83	−	−
48077	20403	0.1	A+S	+50/+52	1/5	2.70/2.48	1.09	−	−
14347	12772	25	S*	+35/+17	0/5	2.20/1.71	1.29	−	−
26980	19256	1.0	S	−12/+47	1/15	0.0/3.52	0.0	+++	+++
26980	19256	0.5	S	+20/+57	3/20	0.13/3.53	0.04	++	+++
26980	19256	0.25	S	+34/+42	0/10	0.27/3.39	0.08	++	++
—	20779	4.0	S	+26/+40	0/10	0.61/1.88	0.32	+	++
—	20779	2.0	S	+27/+41	1/10	0.22/3.06	0.07	++	++
—	28008	2.5	S	−15/+50	3/10	0.0/3.70	0.0	+++	+++
—	28009	1.25	A+S	+22/+65	0/10	0.10/5.32	0.02	++	+++
—	28010	1.25	S	+4/+74	1/10	0.0/4.15	0.0	+++	+++
—	28145	2.5	A+S	+54/+47	0/10	2.27/1.85	1.23	−	−
—	28146	2.5	A+S	−12/+50	4/10	0.0/3.14	0.0	+++	+++
—	28242	5.0	A+S	−14/+49	2/10	0.0/2.79	0.0	+++	+++
524678	24678	2.0	S	+14/+47	1/20	0.64/3.09	0.21	++	±
524678	24678	1.0	S	+29/+43	1/5	3.65/3.73	0.98	−	−
524678	24678	0.5	S	+35/+52	1/5	3.88/4.13	0.94	−	−
3055	12414	75	S	+28/+27	1/5	2.41/3.12	0.77	−	−
3055	12414	50	S	+36/+63	0/5	2.78/3.77	0.74	±	−
64393	14155	125	S	+36/+42	0/5	1.57/1.60	0.98	−	−
105388	17277	2.0	A+S	+44/+72	2/5	5.06/3.92	1.29	−	−
105388	17277	1.0	A+S	+46/+49	1/5	4.32/4.32	1.00	−	−
—	19439	500	S	+56/+64	0/5	3.98/3.22	1.24	−	−
58514	20863	0.05	S*	+33/+54	2/10	3.29/2.77	1.19	−	−
58514	20863	0.025	S*	+48/+53	0/10	1.68/2.85	0.59	±	−
58856	25707	1.25	A+W	+42/+47	0/10	0.56/1.28	0.44	+	−
526417	26417	0.025	A+S	+8/+46	4/10	0.55/1.97	0.28	+	++
526094	26094	0.005	A+S	+50/+46	0/10	2.17/2.81	0.77	−	−
526094	26094	0.0025	A+S	+42/+56	0/10	2.50/3.16	0.79	−	−
525822	25822	0.005	A+S	+32/+37	0/10	0.57/1.48	0.39	+	+
525822	25822	0.0025	A+S	+28/+56	2/10	3.46/3.18	1.09	−	−
24559	20047	0.3	S	+47/+52	0/5	2.70/2.48	1.09	−	−

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
52947	27773	1.0	S*	+41/+48	0/5	3.23/3.55	0.91	–	–
83340	28487	5.0	S	+33/+58	0/25	2.32/3.47	0.67	±	–
65423	9749	5.0	S	+16/+22	1/5	0.76/2.61	0.29	+	+
76029	13328	2,500	S	+20/+23	1/5	2.50/2.64	0.95	–	–
76029	13328	500	S	+22/+22	0/5	2.86/2.61	1.10	–	–
34533	19804	500	CMC	+68/+70	1/10	3.90/4.80	0.81	–	–
39147	20250	0.3	S	+23/+63	1/10	1.92/4.23	0.46	+	±
39147	20250	0.15	S	+41/+50	0/5	2.52/2.89	0.87	–	–
45383	20556	0.2	A+S	−6/+68	2/10	1.65/4.02	0.41	+	±
45383	20556	0.1	A+S	+23/+46	0/5	3.28/3.20	1.03	–	–
521007	21007	0.05	S	+41/+49	1/5	4.31/3.35	1.29	–	–
53104	21568	500	CMC	+18/+52	0/5	1.84/2.44	0.75	±	–
521778+	21778	2,000	S	+44/+46	1/15	2.05/3.02	0.68	±	–
521778	21778	500	S	+47/+42	1/5	3.80/3.81	1.00	–	–
31083	21721	1,000	S	+26/+46	0/5	2.43/3.67	0.66	±	–
31083	21721	250	S	+59/+52	0/10	2.61/3.20	0.82	–	–
526368	26368	1.0	CMC	+32/+24	1/5	1.53/1.51	1.01	–	–
51812	24907	40	CMC*	+45/+35	0/5	2.24/2.60	0.86	–	–
526598	26598	0.125	CMC	+48/+50	0/5	3.55/3.20	1.11	–	–
56410	25021	0.2	S	+8/+27	0/10	0.05/1.94	0.03	++	+++
56410	25021	0.1	S	+8/+35	1/5	1.31/2.90	0.45	+	±
59729	28430	0.5	S	+2/+47	0/5	2.44/2.29	1.07	–	–
59729	28430	0.25	S	+9/+47	0/5	2.98/2.29	1.30	–	–
—	18355	0.05	S*	+63/+67	0/10	4.08/3.54	1.15	–	–
				VII. Quinolines					
3396	2397	75	PG	−1/+60	1/5	3.12/3.45	0.90	–	–
4141	11874	50	CMC	+58/+59	0/5	3.40/2.82	1.21	–	–
346	9408	50	CMC	+55/+66	1/5	2.15/3.50	0.61	±	–
732	14136	75	CMC	+53/+58	1/5	2.73/3.45	0.79	–	–
528997	28997	125	CMC	+65/+62	0/5	2.77/2.99	0.93	–	–
528995	28995	25	CMC	+47/+68	0/5	4.03/3.15	1.28	–	–
528996	28996	0.5	CMC	+70/+68	0/5	4.33/3.15	1.37	–	–
21655	13198	150	S	+30/+28	2/5	2.65/2.44	1.09	–	–
21655	13198	75	S	+33/+58	0/5	3.02/3.45	0.88	–	–
19645	16292	2.5	CMC	+27/+47	2/10	3.30/3.33	0.99	–	–
—	16293	4.0	CMC	+17/+47	0/5	3.04/3.33	0.91	–	–
				VIII. Miscellaneous Compounds					
757	280	0.25	S	+15/+37	0/5	4.43/3.21	1.38	–	–
9170	15025	40	S	+9/+36	2/5	2.80/3.13	0.89	–	–
9170	15025	20	S	+35/+58	0/10	3.89/3.71	1.05	–	–
3096	11626	2.5	S	+35/+36	1/5	4.07/3.00	1.36	–	–
—	19121	10	CMC	+31/+58	0/10	4.36/4.77	0.91	–	–
—	21509	500	S	+55/+44	1/5	3.15/2.54	1.24	–	–
—	21509	250	S	+53/+56	1/10	3.25/3.19	1.02	–	–
46096	3615	62.5	BS	+81/+46	2/5	2.10/3.10	0.68	±	–
13875	1905	125	CMC*	+43/+57	0/5	2.50/3.32	0.76	–	–
525661	25661	2.5	S*	+22/+46	1/15	2.14/2.13	1.00	–	–
4	3844	200	CMC	+45/+49	1/5	4.83/4.05	1.19	–	–
4	3844	75	CMC	+54/+62	0/10	2.84/3.63	0.78	–	–
401593	14071	25	S	+41/+32	0/5	3.93/3.41	1.15	–	–
11926	26153	1.0	S	+30/+33	0/5	1.90/1.43	1.36	–	–
14574	1471	50	S	+37/+54	1/5	2.20/2.95	0.75	±	–
64075	9112	100	CMC	+30/+58	0/5	4.45/3.95	1.12	–	–

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
64074	9113	100	CMC	+50/+58	0/5	4.83/3.95	1.22	–	–
12865	11258	125	CMC	+42/+17	2/5	2.13/1.71	1.25	–	–
3089	14950	15	CMC	+70/+67	0/5	4.51/3.54	1.27	–	–
33963	18766	30	CMC	+13/+43	0/5	3.73/4.27	0.87	–	–
34162	16844	10	S*	+65/+48	0/5	3.59/3.02	1.19	–	–
4730	14406	37.5	S	+49/+48	0/10	3.33/3.80	0.88	–	–
—	13808	250	CMC	+55/+51	0/5	4.08/3.85	1.06	–	–
59354	25627	250	CMC	+21/+39	1/15	1.16/2.15	0.54	±	–
5354	1147	200	S*	+55/+61	0/10	4.43/4.78	0.92	–	–
5354	1147	50	S*	+30/+43	0/5	4.03/4.27	0.94	–	–
8538	19801	15	CMC	+55/+57	0/5	3.78/3.32	1.14	–	–
—	20547	50	CMC	+38/+56	0/5	3.86/2.81	1.37	–	–
525602	25602	6.25	S	+1/+28	1/5	0.70/1.20	0.58	±	–
525602	25602	3.13	S	+29/+26	1/5	1.10/1.26	0.87	–	–
525602	25602	1.5	S	+59/+55	0/5	3.75/4.17	0.90	–	–
522679	22679	500	CMC	+56/+70	0/5	3.94/3.87	1.02	–	–
21666	25825	75	CMC	+39/+52	3/20	2.71/3.27	0.83	–	–
21666	25825	37.5	CMC	+43/+36	0/5	1.94/1.76	1.10	–	–
527516	27516	50	CMC	+16/+59	1/5	2.38/2.72	0.88	–	–
66248	26071	100	CMC*	+48/+35	0/10	0.47/1.35	0.35	+	+++
525442	25442	250	CMC*	+41/+70	2/5	3.62/3.79	0.96	–	–
525442	25442	125	CMC*	+47/+40	0/10	3.62/3.77	0.96	–	–
53582	25513	62.5	CMC*	+23/+49	1/15	0.15/2.86	0.05	++	+++
49403	25512	125	CMC	+33/+48	2/15	0.30/2.73	0.11	++	+++
49403	25512	62.5	CMC	+40/+50	0/15	0.58/3.25	0.18	++	++
—	1380	125	CMC	+56/+57	2/5	5.03/3.67	1.37	–	–
405	23102	250	CMC	+47/+28	1/5	4.51/4.02	1.12	–	–
—	16683	125	CMC	+38/+52	0/5	2.16/2.05	1.05	–	–
23306	26081	60	CMC*	+39/+33	0/5	1.33/1.40	0.95	–	–
2100	384	250	GA	+25/+46	0/5	2.50/3.10	0.81	–	–
522558	22558	500	CMC	+47/+46	0/5	3.27/3.20	1.02	–	–
4463	6938	125	CMC	−11/+56	2/5	2.25/3.93	0.57	±	–
25647	2401	35	CMC	+60/+67	0/5	3.93/4.00	0.98	–	–
34540	24297	150	S	+34/+37	1/5	2.90/3.02	0.96	–	–
—	18999	25	CMC	+53/+61	0/5	2.97/3.64	0.82	–	–
—	22388	200	CMC	+50/+70	1/5	3.60/3.87	0.93	–	–
36539	24298	160	CMC	+24/+37	0/5	3.77/3.02	1.25	–	–
45409	24299	80	CMC	+38/+37	1/5	3.18/3.02	1.05	–	–
—	28239	25	A+S	+23/+49	0/10	0.0/3.25	0.0	+++	+++
—	28265	50	A+S	+58/+59	0/10	1.25/4.76	0.26	+	++
527517	27517	5.0	CMC	+31/+55	2/15	2.74/2.89	0.95	–	–
21206	15928	2.5	CMC	+30/+57	2/5	4.68/3.67	1.28	–	–
522600	22600	30	CMC	+36/+51	1/5	2.70/2.50	1.08	–	–
31659	19453	0.5	S	+54/+71	0/5	3.23/3.80	0.85	–	–
523485	23485	7.5	CMC	+28/+37	1/5	3.46/3.02	1.15	–	–
523484	23484	15	CMC	+31/+37	0/5	3.85/3.02	1.27	–	–
523486	23486	4.0	CMC	+45/+37	0/5	3.96/3.02	1.31	–	–
758	1812	750	S	+27/+46	1/10	2.05/4.09	0.50	+	–
17559	22575	250	CMC	+46/+52	0/5	3.49/3.36	1.04	–	–
—	19918	200	S	+57/+55	0/5	1.36/2.37	0.57	±	–
—	22841	500	S*	+49/+52	1/5	4.40/3.36	1.31	–	–
24854	20895	500	S	+52/+48	2/5	2.27/3.00	0.76	–	–
24854	20895	250	S	+60/+43	1/5	4.46/3.73	1.20	–	–
37538	21569	500	S	+33/+46	0/15	0.04/2.94	0.01	++	+++
54186	24580	25	S*	+41/+40	3/15	2.21/2.96	0.75	±	–

TABLE 4.—Effect of compounds on Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
524784	24784	1.0	S	+20/+40	2/5	0.0/1.40	0.0	+++	+++
524784	24784	0.5	S	+29/+31	0/10	0.53/2.42	0.22	++	++
—	8125	1,000	S	+59/+32	1/10	1.40/3.19	0.44	+	±
521828	21828	250	CMC	+38/+42	0/15	2.29/1.78	1.29	–	–
7786	13943	100	S	+9/+28	0/5	2.38/2.44	0.98	–	–
35843	24759	125	S	+14/+38	0/5	1.32/1.48	0.89	–	–
35847	24760	16	CMC	−4/+46	2/15	2.45/2.09	1.17	–	–
38280	24761	16	S	+28/+41	2/20	1.09/1.50	0.73	±	–
527179	27179	1,000	A+C*	+36/+45	0/15	2.02/3.45	0.59	±	–
3051	8328	250	S	+10/+54	0/10	2.28/2.20	1.04	–	–
32065	22591	100	CMC	+55/+46	0/5	3.05/3.20	0.95	–	–
3095	2917	100	S	+7/+63	1/5	3.65/3.69	0.99	–	–
10924	156	250	CMC	+42/+68	0/5	2.81/4.02	0.70	±	–
746	129	500	S	+26/+48	0/15	2.39/3.85	0.62	±	–
25649	8856	100	CMC	+26/+37	3/15	1.27/3.55	0.36	+	–
25649	8856	50	CMC	+59/+53	0/5	4.10/4.91	0.84	–	–
139	27091	30	CMC	+38/+54	0/5	3.72/3.13	1.19	–	–
27223	16767	150	S*	+38/+48	1/5	5.01/4.52	1.11	–	–
—	16395	100	S*	+47/+66	1/5	3.56/3.50	1.02	–	–
—	16395	50	S*	+42/+44	0/5	3.03/3.23	0.94	–	–
65448	59	1.0cc/rat	GA	+57/+45	1/5	2.85/3.24	0.88	–	–
—	20890	5.0	S*	+58/+50	0/10	0.80/2.34	0.34	+	±
—	20890	2.0	S*	+67/+78	0/5	3.86/4.42	0.87	–	–
—	8800	0.1	S*	+35/+58	0/5	2.55/3.43	0.74	±	–
526741	26741	125	PO	+22/+50	2/5	3.18/2.39	1.33	–	–
526739	26739	500	A+P	+59/+47	0/5	3.72/2.79	1.33	–	–
—	26744	15	PO	+44/+50	0/5	3.09/2.39	1.29	–	–
25648	5326	400	CMC	+90/+67	0/5	3.46/4.00	0.87	–	–
38583	1417	250	S	+29/+42	1/5	4.06/3.39	1.19	–	–
523316	23316	20	CMC	+60/+55	2/5	3.85/4.35	0.89	–	–
523313	23313	10	S	+61/+55	2/5	2.83/4.35	0.65	±	–
523314	23314	8.0	CMC	+64/+49	0/5	4.13/3.35	1.23	–	–
12693	23315	20	CMC	+55/+49	0/5	4.03/3.35	1.20	–	–
44690	1039	7.5	CMC	+44/+70	0/5	4.16/3.87	1.07	–	–
—	2516	500	GA	+50/+28	1/5	5.66/4.48	1.26	–	–
—	18134	25	CMC	+7/+61	1/5	3.01/3.64	0.83	–	–
—	19549	25	CMC	+56/+54	0/5	3.51/2.51	1.40	–	–
9369	20035	10	CMC	+26/+43	0/5	3.25/4.27	0.76	–	–
—	19548	50	CMC	+35/+58	0/5	2.53/3.23	0.78	–	–
526376	26376	4.0	S	+49/+61	1/5	2.13/2.83	0.75	±	–
3070	2800	10	CMC	+10/+50	2/15	2.52/3.09	0.82	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 5.—Effect of compounds on mitomycin C-resistant Jensen sarcoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				1. Alkylating Agents					
762	101	0.25	S*	+20/+59	0/20	2.10/2.74	0.77	–	–
8806	15673	1.0	S*	+37/+68	0/25	2.18/3.33	0.65	±	–

TABLE 5.—Effect of compounds on mitomycin C-resistant Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
525691	25691	12.5	CMC	+25/+59	0/20	2.37/3.46	0.69	±	–
525691	25691	6.25	CMC	+29/+41	0/5	2.31/3.31	0.70	±	–
526407	26407	25	CMC*	+23/+53	1/20	2.66/3.06	0.87	–	–
525823	25823	200	CMC*	−17/+50	3/15	1.86/4.15	0.45	+	–
526622	26622	125	CMC*	+9/+58	0/5	1.88/3.40	0.55	±	–
525022	25022	200	CMC*	−13/+50	3/10	2.58/4.15	0.62	±	–
525022	25022	100	CMC*	+25/+50	0/5	2.02/2.15	0.94	–	–
526406	26406	25	CMC*	−2/+48	5/15	1.94/3.59	0.54	±	–
527453	27453	50	CMC*	+9/+43	1/5	2.65/3.49	0.76	–	–
62403	27456	2.0	CMC*	−21/+41	2/5	1.43/1.52	0.94	–	–
62403	27456	1.0	CMC*	+9/+54	0/5	1.15/2.03	0.57	±	–
62403	27456	0.5	CMC*	+53/+57	1/5	3.18/2.31	1.38	–	–
47774	24591	50	CMC*	+32/+63	1/5	2.45/2.11	1.16	–	–
750	5681	5.0	PO	+43/+60	2/15	3.36/3.34	1.01	–	–
3052	7505	50	PO	+51/+60	1/20	2.39/3.03	0.79	–	–
26271	20501	12.5	S*	+31/+66	0/20	1.89/3.03	0.62	±	–
26271	20501	6.25	S*	+37/+54	0/10	2.44/3.73	0.65	±	–
9706	1133	0.25	S*	+26/+45	2/10	3.65/3.07	1.19	–	–
9706	1133	0.125	S*	+40/+67	2/20	2.79/2.91	0.96	–	–
6396	6882	2.0	S*	+29/+54	1/10	2.02/2.72	0.74	±	–
				II. Pyrimidine Analogs					
19893	18143	25	S	+40/+60	0/15	2.08/2.62	0.79	–	–
27640	19150	40	S	+32/+50	0/10	2.48/2.97	0.84	–	–
				III. Purines and Analogs					
526485	26485	60	PO	+37/+63	1/5	2.91/3.78	0.77	–	–
755	5357	30	CMC	+38/+60	0/15	3.05/2.65	1.15	–	–
743	1395	60	S	+70/+47	0/10	4.60/4.75	0.97	–	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+39/+40	2/10	2.70/2.27	1.19	–	–
739	1072	0.25	S*	+18/+45	1/10	1.90/3.07	0.62	±	–
740	1275	0.75	S*	+34/+50	4/20	2.54/3.07	0.83	–	–
740	1275	0.50	S*	+46/+43	1/5	1.98/2.91	0.68	±	–
740	1275	0.25	S*	+37/+54	0/10	1.77/2.03	0.87	–	–
				V. Steroids					
49420E	2795	37.5	CMC	+4/+45	1/10	3.28/2.99	1.14	–	–
10483E	3047	37.5	CMC	+34/+53	0/5	3.36/3.06	1.10	–	–
9166E	2799	500	CMC	+49/+53	1/5	2.56/3.06	0.84	–	–
20293E	10696	40	CMC	+15/+53	1/5	3.40/3.06	1.11	–	–
				VI. Antibiotics					
185	903	1.0	S	+27/+40	2/5	2.67/2.27	1.18	–	–
185	903	0.25	S	+41/+44	0/5	3.85/3.15	1.22	–	–
3053	14095	0.025	A+S	+48/+45	2/20	2.45/2.58	0.95	–	–
26980	19256	1.0	S	−2/+46	1/10	1.18/3.46	0.34	+	±
26980	19256	0.5	S	+16/+52	4/100	2.68/3.46	0.78	–	–
26980	19256	0.25	S	+21/+48	1/20	3.16/3.47	0.91	–	–
—	20779	4.0	S	−19/+33	1/5	2.45/2.40	1.02	–	–
—	20779	2.0	S	+61/+50	1/5	2.90/2.15	1.35	–	–
58514	20863	0.025	S*	+22/+53	2/10	2.00/1.70	1.18	–	–
58514	20863	0.0125	S*	+50/+52	0/5	3.54/2.94	1.20	–	–
31083	21721	1,000	S	+26/+43	0/10	2.62/2.84	0.92	–	–

TABLE 5.—Effect of compounds on mitomycin C-resistant Jensen sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
51812	24907	20	CMC*	+49/+49	0/5	4.56/4.11	1.11	–	–
526598	26598	0.5	CMC	+47/+44	0/5	2.46/2.64	0.93	–	–
56410	25021	0.1	S	−6/+44	2/10	1.75/3.21	0.55	±	–
				VII. Quinolines					
19645	16292	2.5	CMC	+21/+40	2/10	3.00/2.27	1.32	–	–
				VIII. Miscellaneous Compounds					
9170	15025	20	S	+31/+50	0/5	2.73/2.75	0.99	–	–
525816	25816	50	S	+45/+45	0/5	3.18/3.67	0.87	–	–
525661	25661	5.0	S*	+31/+53	0/10	3.56/3.98	0.89	–	–
14574	1471	25	S	+31/+44	2/10	3.56/3.55	1.00	–	–
59354	25627	250	CMC	+26/+30	1/5	2.65/3.31	0.80	–	–
5354	1147	200	S*	+42/+50	1/10	2.69/2.97	0.91	–	–
5354	1147	100	S*	+26/+44	1/5	3.43/3.94	0.87	–	–
66248	26071	100	CMC*	+46/+30	2/5	3.83/3.31	1.16	–	–
53582	25513	62.5	CMC*	+22/+63	2/5	2.87/3.78	0.76	–	–
49403	25512	62.5	CMC	+29/+51	0/10	2.25/3.22	0.70	±	–
524784	24784	0.5	S	+30/+47	0/5	4.31/4.11	1.05	–	–
3051	8328	125	S	+27/+62	2/5	3.45/3.90	0.88	–	–
746	129	500	S	+37/+61	0/15	2.77/3.47	0.80	–	–
526739	26739	500	A+P	+47/+52	0/5	2.39/3.24	0.74	±	–
526741	26741	62.5	PO	+33/+52	2/5	2.48/3.24	0.77	–	–
—	26744	15	PO	+68/+63	0/5	4.42/3.78	1.17	–	–
7785	8803	100	S	+22/+58	1/5	2.53/3.40	0.74	±	–

*Compound solution or suspension prepared fresh daily.

TABLE 6.—Effect of compounds on sarcoma R39

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	0.5	S*	−15/+45	0/10	0.20/2.15	0.09	++	+++
762	101	0.25	S*	−11/+35	0/20	1.15/2.52	0.46	+	±
10107	598	0.5	S*	−18/+25	1/10	0.07/1.84	0.04	++	++
9506	1424	5.0	PO	−4/+41	3/30	0.74/3.71	0.20	++	+
9506	1424	2.5	PO	+12/+75	0/10	1.04/4.30	0.24	++	±
49421	4614	2.5	S*	+17/+38	0/10	0.0/2.15	0.0	+++	+++
9717	3818	2.5	S	+2/+49	0/20	0.0/1.86	0.0	+++	+++
—	2732	500	S*	+9/+36	1/15	0.88/2.73	0.32	+	++
9706	1133	5.0	S*	−6/+33	2/15	0.04/3.36	0.01	++	+++
9706	1133	2.5	S*	+5/+36	0/10	0.0/4.80	0.0	+++	+++
9706	1133	1.0	S*	+20/+26	1/10	0.0/1.54	0.0	+++	+++
9706	1133	0.5	S*	+17/+28	1/10	0.0/3.10	0.0	+++	+++
9706	1133	0.1	S*	+32/+29	0/25	0.06/2.40	0.03	++	+++
9706	1133	0.05	S*	+41/+38	0/10	0.68/1.61	0.42	+	–
9706	1133	0.01	S*	+38/+38	0/10	1.87/1.61	1.16	–	–
48225	4383	1.5	S*	−30/+35	1/5	0.0/2.30	0.0	+++	+++
48225	4383	1.0	S*	−9/+44	3/25	0.0/2.27	0.0	+++	+++
48225	4383	0.5	S*	+18/+48	0/20	0.03/2.20	0.01	++	+++
48225	4383	0.25	S*	+36/+67	1/10	1.55/1/63	0.95	–	–

TABLE 6.—Effect of compounds on sarcoma R39—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				II. Pyrimidine Analogs					
3277	1336	50	S	+15/+12	0/5	2.89/2.26	1.28	–	–
				III. Purines and Analogs					
749	1150	200	CMC	+8/+29	3/20	2.45/2.31	1.06	–	–
749	1150	125	CMC	+20/+30	0/5	3.35/3.68	0.91	–	–
755	5357	50	CMC	+2/+32	1/10	0.40/1.64	0.24	++	++
743	1395	70	S	−6/+30	2/15	1.30/1.62	0.80	–	–
3057	1054	100	GA	+21/+23	0/5	2.34/4.10	0.57	±	–
				IV. Antimetabolites and Folic Acids					
3073	642	50	S*	+10/+25	0/5	2.33/3.96	0.59	±	–
3073	642	10	S*	+20/+25	0/5	2.62/3.96	0.66	±	–
739	1072	0.25	S*	−5/+33	0/5	1.08/2.52	0.43	+	±
740	1275	1.5	S*	+13/+35	2/10	1.33/2.98	0.45	+	–
740	1275	1.0	S*	−6/+45	3/25	0.85/2.83	0.30	+	–
—	1332	20	S*	+27/+50	0/5	1.76/2.94	0.60	±	–
—	1332	15	S*	+17/+50	0/5	1.87/2.94	0.64	±	–
—	1332	10	S*	+10/+51	0/15	2.72/2.52	1.08	–	–
—	1718	100	CMC	+9/+12	0/5	2.02/2.26	0.89	–	–
—	860	200	S	+10/+12	0/5	2.04/2.26	0.90	–	–
107136	1414	75	S	−22/+30	2/10	2.23/2.53	0.88	–	–
				V. Steroids					
49420E	2795	50	CMC	−17/+43	0/20	1.27/2.53	0.50	+	–
49420E	2795	37.5	CMC	−9/+46	1/10	2.00/3.10	0.65	±	–
—	3092	10	S	−5/+13	2/5	0.85/1.13	0.75	±	–
15468E	3144	250	CMC	+44/+44	1/10	2.43/2.57	0.95	–	–
				VI. Antibiotics					
402815+	2405	2,000	S*	+49/+45	0/5	1.40/2.30	0.61	±	–
14083	4516	500	S	+44/+46	0/5	2.53/2.35	1.08	–	–
3069	2155	500	CMC*	+20/+46	0/5	2.70/3.10	0.87	–	–
13252	1333	50	GA*	+42/+45	1/5	1.50/2.30	0.65	±	–
9169	2859	150	S	+24/+12	0/10	2.15/2.80	0.77	–	–
—	2935	0.5	S	+24/+67	2/5	1.50/1.63	0.92	–	–
				VII. Miscellaneous Compounds					
757	280	0.25	S	+81/+46	2/5	2.27/1.90	1.19	–	–
46096	3615	62.5	BS	+26/+46	1/5	2.10/3.10	0.68	±	–
13875	1905	100	CMC*	+19/+19	2/10	4.42/3.66	1.21	–	–
36390	436	4.0	CMC*	−13/+14	1/5	3.11/2.87	1.08	–	–
36390	436	2.0	GA	−14/+14	0/5	2.92/2.87	1.02	–	–
4794	1356	5.0	S	+22/+60	0/5	1.63/1.74	0.94	–	–
—	1866	10	CMC	+11/+60	1/5	1.25/1.74	0.72	±	–
2100	384	50	GA	+30/+43	0/10	2.43/2.73	0.89	–	–
748	7078	200	PG	+41/+42	0/5	2.44/2.46	0.99	–	–
748	7078	125	PG	+39/+35	0/10	1.85/1.75	1.06	–	–
3051	8328	250	S	+1/+42	2/5	1.58/2.46	0.64	±	–
746	129	1,000	S	−13/+45	0/10	0.70/2.30	0.30	+	–
746	129	500	S	0/+47	1/10	1.15/2.13	0.54	±	–
3769	610	6.0	S	+43/+39	0/5	2.67/2.17	1.23	–	–
4645	5959	50	S	+27/+60	0/5	1.81/1.74	1.04	–	–
—	1185	125	CMC	+38/+39	2/5	1.48/2.17	0.68	±	–
—	2153	100	GA	+13/+37	0/5	3.00/3.61	0.83	–	–
—	7837	175	S	+5/+60	1/5	1.58/1.74	0.91	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 7.—Effect of compounds on Yoshida sarcoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	1.0	S*	+12/+45	0/10	0.0/2.05	0.0	+++	+++
762	101	0.25	S*	+30/+46	0/10	0.0/1.88	0.0	+++	+++
8806	15673	1.0	S*	+44/+60	0/10	0.0/1.27	0.0	+++	+++
525691	25691	12.5	CMC	+39/+51	0/20	0.0/2.36	0.0	+++	+++
526407	26407	25	CMC*	+16/+45	1/10	0.0/1.33	0.0	+++	+++
525823	25823	200	CMC*	−12/+37	1/10	0.0/2.00	0.0	+++	+++
525022	25022	100	CMC*	0/+46	0/10	0.0/1.86	0.0	+++	+++
526406	26406	10	CMC*	+19/+43	0/10	0.0/1.40	0.0	+++	+++
527453	27453	50	CMC*	+19/+45	1/10	0.02/1.63	0.01	++	+++
62403	27456	1.0	CMC*	+7/+42	0/10	0.0/2.54	0.0	+++	+++
62403	27456	0.5	CMC*	+39/+59	0/10	0.0/2.43	0.0	+++	+++
62403	27456	0.25	CMC*	+46/+50	0/15	1.35/3.18	0.42	+	±
62403	27456	0.125	CMC*	+56/+49	0/10	2.25/3.07	0.73	±	−
23909	24464	20	S*	+7/+47	1/15	0.89/3.05	0.29	+	±
409962	27702	8.0	S*	+13/+54	0/10	0.0/2.49	0.0	+++	+++
409962	27702	4.0	S*	+17/+51	0/10	0.0/2.38	0.0	+++	+++
409962	27702	2.0	S*	+35/+46	0/10	0.0/2.80	0.0	+++	+++
409962	27702	1.0	S*	+48/+53	0/10	0.86/2.95	0.29	+	+
409962	27702	0.5	S*	+47/+46	0/5	2.10/2.85	0.74	±	−
3052	7505	50	PO	+26/+44	0/10	0.08/1.64	0.05	++	++
529213	29213	2.5	CMC	+23/+57	1/5	0.0/2.63	0.0	+++	+++
529213	29213	1.0	CMC	+34/+60	0/10	0.0/3.45	0.0	+++	+++
84641	29102	40	CMC	−1/+59	0/10	0.0/3.76	0.0	+++	+++
26271	20501	25	S*	+4/+46	1/10	0.05/1.66	0.03	++	+++
9706	1133	0.125	S*	+26/+47	0/10	0.0/1.98	0.0	+++	+++
528988	28988	10	CMC	−5/+58	1/10	0.0/1.92	0.0	+++	+++
				II. Pyrimidine Analogs					
19893	18143	25	S	+27/+58	1/10	2.55/2.80	0.91	−	−
—	29217	50	CMC	+49/+59	1/5	3.97/3.76	1.06	−	−
				III. Purines and Analogs					
110037	17359	50	CMC	+53/+43	0/5	3.35/3.01	1.11	−	−
527612	27612	10	CMC	+43/+43	0/5	2.44/2.01	1.21	−	−
528403	28403	35	A+C	+52/+43	0/5	2.81/2.01	1.40	−	−
526485	26485	60	PO	+25/+43	1/15	1.03/1.93	0.53	±	−
				IV. Antimetabolites and Folic Acids					
740	1275	1.5	S*	+26/+49	2/10	1.15/1.91	0.60	±	−
740	1275	0.25	S*	+45/+50	0/10	2.81/2.22	1.27	−	−
				V. Steroids					
10483E	3047	37.5	CMC	−6/+78	0/5	1.99/2.60	0.77	−	−
20293E	10696	40	CMC	+14/+69	1/10	0.77/2.00	0.39	+	±
				VI. Antibiotics					
3053	14095	0.025	A+S	+45/+46	0/5	1.86/1.88	0.99	−	−
26980	19256	1.0	S	−1/+45	2/10	0.0/2.33	0.0	+++	+++
26980	19256	0.5	S	+3/+42	0/10	0.12/1.90	0.06	++	+++
—	28010	2.5	S	−10/+69	2/10	0.0/2.91	0.0	+++	+++
—	28145	2.5	A+S	+47/+52	0/10	2.46/2.87	0.86	−	−
—	28146	2.5	A+S	−25/+42	3/10	0.0/2.46	0.0	+++	+++
—	28242	5.0	A+S	−6/+61	2/10	0.0/2.77	0.0	+++	+++

TABLE 7. Effect of compounds on Yoshida sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
58514	20863	0.025	S*	+14/+44	4/15	2.80/2.93	0.96	–	–
58514	20863	0.0125	S*	+33/+34	1/5	2.36/2.93	0.81	–	–
83340	28487	5.0	S*	+30/+47	3/15	3.44/3.27	1.05	–	–
				VII. Quinolines					
528997	28997	12.5	CMC	+45/+49	0/5	2.09/2.69	0.78	–	–
528995	28995	25	CMC	+43/+49	0/5	2.66/2.69	0.99	–	–
528996	28996	2.5	CMC	+56/+64	0/5	2.61/3.09	0.84	–	–
				VIII. Miscellaneous Compounds					
527516	27516	25	CMC	−2/+57	2/5	2.45/2.35	1.04	–	–
527517	27517	5.0	CMC	+37/+57	1/5	3.48/2.35	1.48	–	–
746	129	500	S	+6/+59	0/10	2.36/2.70	0.87	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 8.—Effect of compounds on Moore sarcoma No. 1

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	0.25	S*	+24/+58	0/10	0.28/1.91	0.51	++	++
762	101	0.125	S*	+30/+63	0/10	0.80/1.85	0.43	+	±
762	101	0.0625	S*	+21/+63	1/5	1.15/1.85	0.62	±	–
8806	15673	1.0	S*	+37/+55	0/15	0.32/1.94	0.16	++	–
525691	25691	25	CMC	+2/+52	3/10	0.53/1.93	0.27	+	+++
525691	25691	12.5	CMC	+17/+35	2/20	0.37/2.00	0.19	++	++
525691	25691	6.25	CMC	+29/+28	0/10	0.27/1.50	0.19	++	++
526407	26407	25	CMC*	+20/+62	2/10	0.29/2.35	0.12	++	++
526407	26407	12.5	CMC*	+21/+20	0/10	0.50/1.76	0.28	+	+
525823	25823	100	CMC*	0/+55	1/10	0.36/2.10	0.17	++	++
525823	25823	50	CMC*	+16/+43	1/10	0.36/2.10	0.17	++	++
526622	26622	250	CMC*	−10/+30	2/10	0.46/1.87	0.25	++	++
526622	26622	125	CMC*	+9/+42	0/5	0.49/2.26	0.22	++	++
525022	25022	200	CMC*	−9/+52	1/15	0.34/1.74	0.20	++	++
526406	26406	25	CMC*	+4/+56	2/15	0.49/2.11	0.23	++	++
527453	27453	50	CMC*	−16/+42	3/10	0.40/1.89	0.21	++	++
62403	27456	1.0	CMC*	−5/+43	0/10	0.71/2.19	0.32	+	±
62403	27456	0.5	CMC*	+45/+60	0/10	1.77/2.40	0.74	±	–
47774	24591	15	CMC*	+39/+48	1/10	0.65/2.59	0.25	++	+
26271	20501	25	S*	+3/+55	2/10	0.71/2.22	0.32	+	+
26271	20501	12.5	S*	+21/+45	2/15	0.59/1.71	0.35	+	+
9706	1133	0.25	S*	+40/+88	1/10	0.33/2.55	0.13	++	++
9706	1133	0.125	S*	+37/+62	0/10	0.49/2.20	0.22	++	++
9706	1133	0.0625	S*	+55/+62	1/10	0.35/2.20	0.16	++	++
9706	1133	0.0312	S*	+49/+62	1/5	0.47/2.20	0.21	++	++
				II. Pyrimidine Analogs					
27640	19150	40	S	+27/+42	0/10	1.50/1.87	0.80	–	–
48006	20000	25	S	+21/+42	2/10	0.73/1.87	0.39	+	–

TABLE 8.—Effect of compounds on Moore sarcoma No. 1—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
48006	20000	10	S	+39/+41	0/5	1.06/1.96	0.54	±	–
				III. Purines and Analogs					
526485	26485	60	PO	+8/+53	2/10	0.99/1.89	0.52	±	–
755	5357	30	CMC	+58/+71	2/10	1.91/1.64	1.16	–	–
56408	26996	0.375	S	0/+54	4/15	1.07/1.96	0.55	±	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+34/+62	0/10	1.55/1.69	0.92	–	–
739	1072	0.125	S*	+21/+41	1/5	2.57/1.96	1.31	–	–
740	1275	0.5	S*	+48/+61	0/10	1.66/1.52	1.09	–	–
				V. Steroids					
10483E	3047	37.5	CMC	+25/+71	1/5	2.11/1.64	1.29	–	–
9166E	2799	500	CMC	+49/+28	2/10	2.66/1.93	1.38	–	–
20293E	10696	40	CMC	0/+62	0/5	2.38/2.37	1.00	–	–
				VI. Antibiotics					
185	903	1.0	S	+23/+56	2/10	0.22/1.67	0.13	++	++
185	903	0.5	S	+30/+68	0/10	0.78/1.97	0.40	+	±
185	903	0.25	S	+37/+68	0/5	1.16/1.97	0.59	±	±
3053	14095	0.025	A+S	+45/+58	0/10	1.48/1.86	0.80	–	–
26980	19256	1.0	S	−10/+63	0/15	0.29/1.94	0.15	++	+++
26980	19256	0.5	S	+5/+68	0/10	0.27/1.97	0.14	++	++
26980	19256	0.025	S	+25/+68	0/5	0.84/1.97	0.43	+	±
524678	24678	2.0	S	+23/+53	0/15	1.60/2.18	0.73	±	–
524678	24678	1.0	S	+38/+21	0/5	1.77/2.18	0.81	–	–
58514	20863	0.025	S*	+14/+37	1/15	2.06/2.12	0.97	–	–
58856	25707	1.25	A+W	+49/+56	0/5	2.22/2.32	0.96	–	–
526417	26417	0.025	A+S	+38/+65	0/10	1.90/2.50	0.76	–	–
526094	26094	0.0025	A+S	+20/+28	0/5	1.40/1.58	0.89	–	–
525822	25822	0.005	A+S	+44/+56	0/5	2.43/2.32	1.05	–	–
526368	26368	1.0	CMC	+26/+28	0/5	1.46/1.58	0.92	–	–
51812	24907	40	CMC*	+37/+38	0/5	1.18/1.47	0.80	–	–
526598	26598	0.125	CMC	+41/+50	0/5	1.75/1.64	1.07	–	–
				VII. Miscellaneous Compounds					
9170	15025	20	S	+19/+68	2/10	1.47/2.36	0.62	±	–
14574	1471	50	S	+34/+62	1/5	2.06/2.37	0.87	–	–
59354	25627	250	CMC	+33/+52	0/5	1.49/1.93	0.77	–	–
5354	1147	200	S*	+30/+28	1/5	2.05/1.93	1.06	–	–
525602	25602	12.5	S	+80/+50	0/5	1.61/1.75	0.92	–	–
66248	26071	100	CMC*	+31/+50	1/10	0.39/2.26	0.17	++	++
49403	25512	62.5	CMC	+31/+35	0/10	0.64/1.70	0.38	+	+
24854	20895	1,000	S	+18/+48	0/5	1.70/1.75	0.97	–	–
54186	24580	25	S*	+32/+48	0/5	2.25/1.75	1.29	–	–
3051	8328	250	S	+15/+67	2/10	1.68/2.36	0.71	±	–
746	129	500	S	+34/+42	2/10	0.38/1.53	0.25	++	++
746	129	250	S	+32/+41	2/5	0.45/1.68	0.27	+	+
746	129	125	S	+13/+41	0/5	2.06/1.68	1.23	–	–
526741	26741	31.25	PO	+60/+51	0/5	2.36/2.08	1.13	–	–
526739	26739	500	A+P	+65/+51	0/5	2.38/2.08	1.14	–	–
—	26744	15	PO	+53/+51	0/5	2.08/2.08	1.00	–	–
523316	23316	20	CMC	+55/+61	0/5	1.34/1.52	0.88	–	–
523314	23314	8.0	CMC	+46/+61	0/5	1.88/1.52	1.24	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				1. Alkylating Agents					
762	101	0.5	S*	−16/+29	2/15	2.29/3.07	0.75	±	−
762	101	0.25	S*	+7/+39	0/20	2.55/3.07	0.83	−	−
10107	598	1.5	S*	−14/+34	2/15	2.48/2.99	0.83	−	−
9506	1424	5.0	PO	−14/+34	0/5	4.25/5.09	0.83	−	−
8806	15673	1.0	S*	+40/+55	1/15	2.43/2.63	0.92	−	−
—	20598	1.0	S*	+44/+46	0/10	1.51/3.24	0.47	+	−
—	20597	1.0	S*	+45/+53	0/10	2.62/2.83	0.93	−	−
525691	25691	12.5	CMC	+40/+45	0/5	2.81/3.31	0.85	−	−
526407	26407	25	CMC*	+18/+34	2/10	2.64/3.00	0.88	−	−
525823	25823	200	CMC*	−21/+45	2/5	0.80/3.31	0.24	++	±
525823	25823	50	CMC*	+14/+25	0/10	0.75/3.39	0.22	++	+
525022	25022	200	CMC*	−23/+44	2/10	0.27/3.36	0.08	++	++
526406	26406	25	CMC*	+10/+43	0/20	1.80/2.77	0.65	±	−
527453	27453	50	CMC*	+9/+47	1/20	2.65/3.55	0.75	±	−
62403	27456	2.0	CMC*	−1/+45	0/5	1.62/4.44	0.36	+	−
62403	27456	1.0	CMC*	+9/+47	1/10	3.01/4.04	0.75	±	−
62403	27456	0.5	CMC*	+29/+33	1/5	3.55/3.85	0.92	−	−
23909	24464	20	S*	−1/+38	2/10	2.35/3.34	0.70	±	−
409962	27702	8.0	S*	−3/+34	2/10	3.43/3.98	0.86	−	−
409962	27702	4.0	S*	+4/+30	1/15	1.91/3.00	0.64	±	−
409962	27702	2.0	S*	+25/+37	0/5	1.87/2.31	0.81	−	−
26750	12066	500	S	+46/+44	0/5	4.15/3.68	1.13	−	−
41269	11088	60	CMC*	+44/+50	0/5	1.66/2.58	0.64	±	−
47774	24591	100	CMC*	−17/+41	2/10	0.31/3.12	0.10	++	++
47774	24591	20	CMC*	+15/+33	0/5	1.56/3.12	0.50	+	±
74437	13595	30	CMC*	+30/+48	0/5	4.09/5.84	0.70	±	−
17016	6699	250	CMC	−3/+43	2/10	2.98/3.84	0.78	−	−
17016	6699	100	CMC	+5/+32	2/10	4.13/4.43	0.94	−	−
750	5681	15	PO	−10/+27	2/5	1.28/3.63	0.35	+	−
750	5681	10	PO	+9/+39	1/15	2.68/4.11	0.65	±	−
750	5681	5.0	PO	+20/+47	2/10	4.28/4.48	0.96	−	−
3052	7505	100	PO	+14/+46	0/5	3.71/4.84	0.77	−	−
3052	7505	50	PO	+23/+38	2/15	3.30/3.72	0.89	−	−
529213	29213	1.0	CMC	+31/+29	0/5	3.79/4.60	0.82	−	−
84641	29102	40	CMC	+10/+54	0/10	1.19/2.81	0.42	+	−
3094	11687	50	PO	+1/+37	3/10	3.93/4.46	0.88	−	−
3094	11687	25	PO	+12/+37	1/5	3.43/3.72	0.92	−	−
408428	14405	250	CMC	−14/+28	2/5	3.73/4.51	0.83	−	−
48821	15128	50	S	+5/+15	2/5	3.53/3.24	1.09	−	−
136059	7503	35	PO	+6/+21	1/5	3.99/3.87	1.03	−	−
—	15749	250	PO	+25/+43	2/15	4.08/4.55	0.90	−	−
—	15749	125	PO	+31/+37	0/5	3.39/3.72	0.91	−	−
49421	4614	1.0	S*	+31/+34	2/15	3.44/4.19	0.82	−	−
9717	3818	1.0	S	+31/+38	3/15	5.06/4.49	1.13	−	−
26271	20501	50	S*	−15/+47	4/10	0.35/3.57	0.10	++	+++
26271	20501	25	S*	+6/+42	6/25	1.49/4.04	0.37	+	+
26271	20501	12.5	S*	+22/+53	1/10	1.68/4.36	0.39	+	+
520644	20644	10	CMC*	+21/+50	2/5	3.50/4.34	0.81	−	−
520645	20645	50	CMC*	+30/+52	0/5	2.92/2.82	1.04	−	−
520646	20646	15	CMC*	+33/+38	0/10	1.68/4.15	0.40	+	−
520647	20647	20	CMC*	+29/+38	0/5	2.92/4.15	0.70	±	−
42158	17360	20	S*	+22/+32	0/5	2.40/2.20	1.09	−	−
—	15385	5.0	S*	−1/+8.0	1/5	3.52/3.54	0.99	−	−

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
—	15385	2.5	S*	+22/+32	0/5	2.00/2.20	0.91	–	–
9706	1133	0.25	S*	+14/+36	2/20	2.89/3.73	0.77	–	–
9706	1133	0.1	S*	+12/+19	4/20	1.83/2.94	0.62	±	–
9706	1133	0.05	S*	+11/+19	2/20	1.91/1.96	0.97	–	–
6396	6882	2.0	S*	+18/+38	2/40	3.36/4.42	0.76	–	–
6396	6882	1.0	S*	+23/+35	1/10	4.24/4.38	0.97	–	–
528988	28988	10	CMC	+24/+41	1/15	2.37/4.38	0.54	±	–
48225	4383	0.5	S*	+10/+34	1/5	1.38/2.36	0.58	±	–
				II. Pyrimidine Analogs					
19593	18143	25	S	+11/+39	0/5	2.50/4.07	0.61	±	–
19893	18143	17.5	S	+16/+46	1/5	3.96/5.14	0.77	–	–
3425	13056	500	CMC	+45/+45	0/5	4.81/4.52	1.06	–	–
529351	29423	50	CMC	+31/+38	0/5	2.58/2.69	0.96	–	–
1589	11770	250	S	+34/+34	0/5	4.61/5.11	0.90	–	–
73376	6959	400	S	+25/+29	0/5	4.13/3.94	1.05	–	–
146604	19273	5.0	S	+9/+28	0/5	3.71/3.43	1.08	–	–
27640	19150	40	S	+36/+41	1/10	3.55/3.69	0.96	–	–
31712	18354	20	S	+29/+45	0/5	4.45/4.63	0.96	–	–
—	29511	60	CMC	+13/+24	0/5	4.03/2.93	1.38	–	–
—	29217	50	CMC	+30/+41	0/5	3.47/3.55	0.98	–	–
48006	20000	10	S	+17/+46	1/10	3.40/4.64	0.73	±	–
—	6883	2.0	S	+28/+40	0/10	4.56/4.28	1.07	–	–
				III. Purines and Analogs					
14666	1387	100	GA	+3/+37	0/5	3.72/4.91	0.76	–	–
3702	1493	125	CMC	+47/+37	0/5	4.64/4.91	0.94	–	–
14664	1494	250	GA	+40/+42	0/5	3.89/4.86	0.80	–	–
110037	17359	50	CMC	+28/+73	1/5	4.00/3.41	1.17	–	–
527612	27612	10	CMC	+43/+30	0/5	3.85/3.98	0.97	–	–
528403	28403	35	A+C	+28/+30	0/5	3.95/3.98	0.99	–	–
—	29830	35	CMC	+24/+28	0/5	2.41/3.59	0.67	±	–
749	1150	150	CMC	−11/+33	1/5	3.25/4.10	0.79	–	–
—	19994	10	S	+21/+35	0/5	3.27/3.59	0.91	–	–
753	8709	250	S	−2/+33	1/5	3.09/4.10	0.75	±	–
744	6048	150	CMC	+16/+35	1/5	4.06/5.84	0.70	±	–
77640	7347	20	CMC	+12/+41	4/15	3.29/4.20	0.78	–	–
77640	7347	15	CMC	−19/+16	0/5	2.63/3.62	0.73	±	–
—	30002	62.5	CMC	+4/+35	0/5	2.74/3.70	0.74	±	–
513473	13473	150	S	−3/+21	2/5	3.08/3.87	0.80	–	–
513473	13473	100	S	+16/+15	1/5	3.70/3.24	1.14	–	–
526180	26180	60	CMC*	+8/+33	0/5	3.31/3.85	0.86	–	–
526485	26485	60	PO	+13/+32	6/15	1.36/1.83	0.74	±	–
755	5357	50	CMC	+18/+28	2/10	2.10/2.64	0.80	–	–
755	5357	35	CMC	+45/+38	0/5	3.65/3.42	1.07	–	–
755	5357	30	CMC	+14/+46	0/25	3.11/3.93	0.79	–	–
755	5357	20	CMC	+40/+42	3/15	3.53/3.99	0.88	–	–
528013	28013	250	S	−3/+42	2/5	3.05/2.61	1.17	–	–
38887	20355	10	CMC	−10/+42	0/5	1.66/4.54	0.37	+	–
39084	20354	100	CMC	+5/+35	1/5	2.58/4.50	0.57	±	–
743	1395	60	S	0/+27	1/5	2.88/4.39	0.66	±	–
752	5459	3.0	CMC	−2/+24	5/30	3.10/3.72	0.83	–	–
58385	14377	15	CMC	+20/+26	1/10	3.37/3.76	0.90	–	–
759	1509	125	S	+26/+42	0/5	2.59/4.82	0.54	±	–
25652	17902	125	CMC	+17/+50	2/5	3.15/4.34	0.73	±	–

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
3057	1054	100	CMC	+11/+41	1/5	3.80/4.80	0.79	–	–
25165	18094	100	S	+28/+25	1/10	3.34/3.66	0.91	–	–
4911	12355	100	CMC	+3/+22	1/5	2.48/3.29	0.75	±	–
520950	20950	50	PO	+21/+35	2/5	3.25/3.24	1.00	–	–
29422	18615	2.5	CMC	+7/+34	1/5	3.48/4.55	0.76	–	–
—	4901	200	GA	+24/+32	2/5	2.88/3.36	0.86	–	–
529509	29509	300	CMC	+8/+35	0/5	0.17/1.84	0.09	++	++
529509	29509	200	CMC	+31/+48	0/10	0.17/3.96	0.04	++	+++
529509	29509	100	CMC	+29/+38	0/5	1.00/3.41	0.29	+	++
				IV. Antimetabolites and Folic Acids					
742	9505	5.0	S*	−12/+60	2/5	1.47/3.82	0.38	+	–
742	9505	2.5	S*	+30/+42	2/20	2.45/3.92	0.63	±	–
742	9505	1.25	S*	+15/+19	1/5	2.14/3.55	0.60	±	–
742	9505	0.63	S*	+22/+35	1/10	5.08/4.40	1.15	–	–
7365	13835	0.05	S*	+34/+21	1/10	3.94/3.68	1.07	–	–
7365	13835	0.025	S*	+41/+37	0/5	5.17/4.19	1.23	–	–
1393	13148	15	CMC	−2/+40	2/10	4.05/3.48	1.16	–	–
5197	13640	5.0	CMC	+29/+35	0/5	2.19/3.56	0.62	±	–
—	1833	400	CMC	+10/+45	0/5	1.73/3.34	0.52	±	–
3073	642	50	S*	+25/+25	1/10	4.49/3.64	1.23	–	–
3073	642	37.5	S*	+47/+34	1/5	4.99/5.09	0.98	–	–
739	1072	0.25	S*	+17/+32	10/25	0.45/2.82	0.16	++	++
739	1072	0.15	S*	+23/+20	1/15	0.78/3.71	0.21	++	±
740	1275	1.5	S*	+4/+33	6/15	0.41/4.00	0.10	++	++
740	1275	1.0	S*	+28/+21	4/10	0.41/3.35	0.12	++	+
740	1275	0.5	S*	+35/+57	2/15	1.45/3.55	0.41	+	–
740	1275	0.25	S*	+56/+66	0/5	2.44/3.64	0.67	±	–
740	1275	0.125	S*	+52/+66	0/5	4.26/3.64	1.17	–	–
—	24813	3.0	CMC	+11/+31	1/10	1.53/1.39	1.10	–	–
—	24815	1.5	CMC	+33/+36	1/10	2.11/1.99	1.06	–	–
				V. Steroids					
49420E	2795	37.5	CMC	−9/+27	2/10	2.87/4.39	0.65	±	–
49420E	2795	25	CMC	+9/+33	2/10	3.48/2.99	1.17	–	–
10483E	3047	37.5	CMC	+10/+50	0/15	2.80/4.03	0.69	±	–
12600E	15347	3.0	CMC	−5/+32	3/15	2.93/3.93	0.75	±	–
12600E	15347	1.5	CMC	+11/+32	0/10	3.29/3.95	0.83	–	–
12601E	18062	5.0	CMC	−8/+35	3/10	2.52/4.32	0.58	±	–
9166E	2799	500	CMC	+35/+47	0/20	3.61/4.10	0.88	–	–
9565E	2931	375	CMC	+32/+34	0/5	3.12/4.32	0.72	±	–
9564E	17653	500	CMC	+11/+21	1/5	2.96/4.21	0.70	±	–
3351E	17469	375	CMC	+20/+40	0/5	3.26/4.31	0.76	–	–
10704E	16816	375	CMC	+26/+35	1/5	4.09/3.90	1.05	–	–
12198E	21102	500	CMC	+37/+60	0/5	3.79/4.47	0.85	–	–
—	3092	10	S	−11/+45	1/5	3.34/4.84	0.69	±	–
20293E	10696	40	CMC	+15/+39	0/10	3.14/3.91	0.80	–	–
20293E	10696	20	CMC	+7/+12	0/5	3.26/3.71	0.88	–	–
20293E	10696	10	CMC	+5/+21	0/5	4.07/4.21	0.97	–	–
23759E	20379	500	CMC	+45/+40	0/5	4.28/4.28	1.00	–	–
				VI. Antibiotics					
402815+	2405	2000	S*	−1/+27	1/5	3.93/4.39	0.90	–	–
14083	4516	500	S	+17/+27	1/5	4.57/4.39	1.04	–	–
3069	2155	500	CMC*	+42/+31	1/5	4.55/5.15	0.88	–	–

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
13252	1333	50	GA*	+32/+33	0/5	4.00/4.10	0.98	−	−
9169	2859	150	S	+15/+31	1/5	4.24/5.15	0.82	−	−
185	903	1.0	S	+6/+38	5/15	3.43/3.86	0.89	−	−
17257	17442	1.25	S	+16/+39	0/5	3.46/4.48	0.77	−	−
—	2163	12.5	CMC	−6/+28	1/5	1.86/4.70	0.40	+	−
3067	2662	15	CMC	+9/+26	1/5	1.96/3.79	0.52	±	−
3067	2662	7.5	CMC	+9/+59	0/5	3.11/3.22	0.97	−	−
—	2935	0.5	S	+6/+38	1/5	3.10/3.42	0.91	−	−
400978	4996	0.5	S	+9/+31	5/15	2.54/3.78	0.67	−	−
9168	6258	10	CMC	+8/+38	3/10	2.00/4.57	0.44	+	−
9168	6258	5.0	CMC	+21/+37	0/10	3.02/3.57	0.85	−	−
58368	13617	50	CMC*	+27/+39	0/5	3.59/3.82	0.92	−	−
18268	11822	0.025	A+S	+17/+45	1/10	3.35/3.83	0.87	−	−
3053	14095	0.05	A+S	+25/+42	1/5	4.78/4.79	1.00	−	−
3053	14095	0.025	A+S	+38/+44	2/15	4.19/4.10	1.02	−	−
14347	12772	250	S*	+23/+27	0/5	4.71/4.98	0.95	−	−
26980	19256	1.0	S	+10/+47	2/25	3.17/4.03	0.79	−	−
26980	19256	0.5	S	+24/+54	0/10	3.70/4.53	0.82	−	−
26980	19256	0.25	S	+27/+47	0/10	3.57/3.97	0.90	−	−
—	20779	2.0	S	+37/+29	0/5	2.81/3.94	0.71	±	−
—	28145	2.5	A+S	+47/+37	0/10	4.14/3.63	1.14	−	−
—	28146	2.5	A+S	−15/+41	4/15	0.88/3.62	0.24	++	−
—	28242	5.0	A+S	−9/+53	2/10	1.55/5.05	0.31	+	−
524678	24678	2.0	S	+11/+44	1/15	2.80/3.52	0.79	−	−
3055	12414	50	S	+20/+31	0/5	2.36/4.32	0.54	±	−
64393	14155	125	S	+32/+33	0/5	3.31/3.31	1.00	−	−
105388	17277	2.0	A+S	+27/+16	1/5	3.44/3.23	1.07	−	−
105388	17277	1.0	A+S	+27/+18	0/5	4.84/3.54	1.37	−	−
—	19439	500	S	+41/+51	0/5	4.46/4.53	0.98	−	−
58514	20863	0.025	S*	+1/+5	2/5	2.02/2.66	0.76	−	−
58856	25707	1.25	A+W	+19/+42	0/5	2.51/3.29	0.76	−	−
526417	26417	0.025	A+S	+21/+55	1/5	1.90/3.25	0.58	±	−
526417	26417	0.0125	A+S	+18/+54	1/5	2.58/3.55	0.73	±	−
526094	26094	0.0025	A+S	+46/+55	0/10	2.95/3.40	0.87	−	−
525822	25822	0.005	A+S	+32/+33	0/5	2.77/3.31	0.84	−	−
525822	25822	0.0025	A+S	+41/+57	0/5	3.46/3.45	1.00	−	−
59729	28430	0.25	S	+3/+25	0/5	2.59/3.39	0.76	−	−
83340	28487	5.0	S	+16/+41	2/10	3.09/4.14	0.75	±	−
76029	13328	500	S	+15/+18	0/5	1.63/3.08	0.53	±	−
34533	19804	500	CMC	+33/+49	1/10	3.66/3.35	1.09	−	−
39147	20250	0.3	S	+16/+33	0/5	3.79/3.61	1.05	−	−
39147	20250	0.15	S	+10/+21	0/5	4.02/4.17	0.96	−	−
45383	20556	0.1	A+S	+6/+38	1/10	3.48/3.48	1.00	−	−
521007	21007	0.05	S	+4/+45	1/5	2.90/3.68	0.79	−	−
53104	21568	500	CMC	+28/+53	2/5	3.40/3.01	1.13	−	−
31083	21721	1000	S	+35/+48	0/10	3.34/4.21	0.79	−	−
526368	26368	1.0	CMC	−11/+33	2/10	2.28/2.62	0.87	−	−
51812	24907	80	CMC*	+19/+38	3/15	1.87/3.22	0.58	±	−
51812	24907	40	CMC*	+47/+38	1/5	2.93/3.56	0.82	−	−
—	1732	20	S	+8/+31	1/5	3.25/4.68	0.69	±	−
526598	26598	0.25	CMC	+12/+29	2/5	2.33/2.18	1.07	−	−
—	30133	5.0	CMC	−2/+35	2/10	0.73/3.24	0.23	++	+
—	30133	2.5	CMC	+20/+43	0/5	0.82/2.35	0.35	+	±
—	18355	0.05	S*	+42/+47	2/10	4.56/4.29	1.06	−	−

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				VII. Quinolines					
3396	2397	75	PG	+26/+34	1/5	3.95/3.85	1.03	–	–
4141	11874	50	CMC	+31/+45	0/5	4.13/4.20	0.98	–	–
346	9408	50	CMC	+61/+45	2/5	4.14/4.20	0.99	–	–
732	14136	50	CMC	+32/+63	2/5	4.69/4.60	1.02	–	–
528997	28997	12.5	CMC	+1/+4	1/5	2.14/2.24	0.96	–	–
528995	28995	25	CMC	+18/+30	0/5	3.52/4.44	0.79	–	–
529105	29105	15	CMC	+12/+11	0/5	2.49/3.01	0.83	–	–
528996	28996	2.5	CMC	+40/+44	0/5	4.67/4.30	1.09	–	–
529103	29103	2.0	CMC	+20/+11	0/5	3.65/3.01	1.21	–	–
21655	13198	75	S	+13/+31	1/5	3.62/4.68	0.77	–	–
19645	16292	2.5	CMC	+39/+63	1/10	4.19/4.60	0.91	–	–
—	16293	8.0	CMC	−7/+37	4/10	1.85/4.35	0.43	+	–
—	16293	4.0	CMC	+28/+45	0/5	3.76/4.20	0.90	–	–
529104	29104	25	CMC	+32/+49	0/5	3.04/4.41	0.69	±	–
				VIII. Miscellaneous Compounds					
757	280	0.25	S	0/+26	2/10	3.71/3.85	0.96	–	–
9170	15025	20	S	+33/+49	2/15	3.29/4.63	0.71	±	–
—	19121	10	CMC	+39/+48	0/5	4.53/4.63	0.98	–	–
—	21509	250	S	+36/+16	0/5	2.91/3.77	0.77	–	–
525816	25816	50	S	+73/+34	0/5	4.75/3.56	1.33	–	–
4	3844	200	CMC	+39/+48	0/5	1.53/2.63	0.58	±	–
4	3844	150	CMC	+24/+34	1/5	4.73/3.69	1.28	–	–
401593	14071	25	S	+47/+51	0/5	4.59/4.71	0.97	–	–
—	1866	10	CMC	−11/+38	3/10	1.94/3.59	0.54	±	–
—	1866	5.0	CMC	+48/+59	0/10	3.06/3.07	1.00	–	–
4794	1356	5.0	S	+49/+44	0/5	3.44/2.92	1.18	–	–
14574	1471	50	S	+30/+50	0/5	3.87/4.84	0.80	–	–
67574	26327	0.125	S	−7/+38	2/20	1.75/3.39	0.51	±	–
64075	9112	100	CMC	+16/+46	0/5	3.69/4.16	0.89	–	–
64074	9113	100	CMC	+41/+46	0/5	3.58/4.16	0.86	–	–
12865	11258	125	CMC	+36/+27	0/5	5.14/4.97	1.03	–	–
34162	16844	10	S*	+16/+22	2/5	3.40/3.29	1.03	–	–
4730	14406	37.5	S	+18/+37	4/15	3.48/4.06	0.86	–	–
—	1577	100	PG	+41/+46	0/5	3.74/4.84	0.77	–	–
59354	25627	250	CMC	+19/+48	0/5	2.85/3.42	0.83	–	–
5354	1147	200	S*	+19/+31	2/10	3.67/3.74	0.98	–	–
5354	1147	50	S*	+12/+42	0/5	4.45/4.84	0.92	–	–
—	20547	50	CMC	+34/+42	0/5	4.10/2.91	1.41	–	–
522679	22679	500	CMC	+39/+50	0/5	3.21/2.58	1.24	–	–
527516	27516	25	CMC	+5/+50	2/10	1.86/3.14	0.59	±	–
66248	26071	100	CMC*	+17/+42	2/5	2.35/3.29	0.71	±	–
66248	26071	50	CMC*	+27/+34	0/5	2.03/2.80	0.73	±	–
525442	25442	125	CMC	+32/+52	2/5	5.20/4.01	1.30	–	–
53582	25513	62.5	CMC*	−18/+31	0/10	1.33/2.75	0.48	+	–
53582	25513	30	CMC*	+45/+57	0/5	3.01/3.45	0.87	–	–
49403	25512	125	CMC	+24/+41	1/10	2.45/2.76	0.89	–	–
49403	25512	62.5	CMC	+62/+54	0/5	4.19/3.55	1.18	–	–
—	1380	125	CMC	+14/+14	0/5	2.78/3.31	0.84	–	–
—	16683	125	CMC	+28/+37	2/10	2.83/4.19	0.68	±	–
23306	26081	60	CMC*	+38/+34	0/5	2.33/2.80	0.84	–	–
522558	22558	500	CMC	+31/+52	0/5	3.08/2.82	1.09	–	–
4463	6938	125	CMC	−11/+39	1/5	2.08/3.17	0.66	±	–
25647	2401	17.5	CMC	+41/+44	0/5	4.64/3.68	1.26	–	–

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
—	18999	25	CMC	+54/+37	1/5	3.86/4.07	0.95	–	–
—	22388	200	CMC	+24/+50	0/5	2.36/2.58	0.91	–	–
—	28239	25	CMC	+19/+32	0/5	2.52/3.21	0.79	–	–
—	28265	50	A+S	+26/+42	0/5	3.59/3.91	0.92	–	–
527517	27517	10	CMC	+24/+50	1/5	2.78/3.35	0.83	–	–
522600	22600	30	CMC	+39/+49	0/5	2.85/2.92	0.98	–	–
31659	19453	0.5	S	+30/+42	0/5	2.15/2.60	0.83	–	–
523485	23485	15	CMC	+19/+42	0/5	3.24/3.28	0.99	–	–
523484	23484	30	CMC	+6/+27	1/10	2.57/2.89	0.89	–	–
17559	22575	250	CMC	+37/+66	0/5	2.67/3.64	0.73	±	–
—	16395	100	S*	+38/+48	1/5	3.94/3.18	1.24	–	–
24854	20895	1.0	S	+22/+41	0/5	3.50/3.12	1.12	–	–
54186	24580	25	S*	+50/+41	0/5	3.60/3.12	1.15	–	–
—	20497	250	S	+12/+38	0/5	3.79/4.92	0.77	–	–
—	8125	1000	S	+36/+59	1/5	3.38/2.73	1.24	–	–
7786	13943	100	S	+31/+48	1/5	3.52/3.15	1.12	–	–
109229	30000	5000 IU	S	+31/+35	0/5	3.50/3.87	0.90	–	–
109229	30000	167 IU	S	+40/+35	0/5	3.72/3.21	1.16	–	–
35843	24759	125	S	+19/+40	0/5	3.20/3.22	0.99	–	–
35847	24760	16	CMC	−6/+37	2/10	2.02/2.89	0.70	±	–
35847	24760	8.0	CMC	+10/+31	1/5	3.11/2.25	1.38	–	–
38280	24761	16	S	+21/+40	0/5	3.59/3.22	1.11	–	–
527179	27179	1000	A+C*	+22/+49	3/10	4.33/3.80	1.14	–	–
748	7078	200	PG	+26/+27	0/5	4.16/3.68	1.13	–	–
748	7078	125	PG	+48/+45	0/5	2.60/3.39	0.77	–	–
3051	8328	250	S	+5/+37	4/20	3.80/3.94	0.96	–	–
3051	8328	150	S	+5/+30	2/15	4.27/3.83	1.11	–	–
32065	22591	200	CMC	+13/+43	1/5	2.04/3.85	0.53	±	–
3095	2917	100	S	+8/+35	1/10	3.98/5.43	0.73	±	–
746	129	500	S	+22/+37	1/10	3.71/4.09	0.91	–	–
3769	610	6.0	S	+12/+21	2/10	3.44/3.14	1.10	–	–
25649	8856	50	CMC	+35/+44	0/5	3.59/3.68	0.98	–	–
30418	16850	250	CMC	+33/+23	0/5	3.62/4.84	0.75	±	–
27223	16767	150	S*	+38/+35	0/5	3.75/3.91	0.96	–	–
—	8800	0.1	S*	+18/+26	1/5	3.72/3.42	1.09	–	–
526741	26741	31.5	PO	+36/+36	0/5	2.05/1.75	1.17	–	–
526739	26739	500	A+P	+1/+3	2/5	1.87/1.63	1.15	–	–
—	26744	15	PO	+27/+44	0/5	1.69/1.75	0.97	–	–
25648	5326	50	CMC	+27/+35	0/5	3.67/2.70	1.36	–	–
38583	1417	250	S	+47/+50	0/5	3.80/2.58	1.47	–	–
523316	23316	20	CMC	+60/+49	0/5	5.25/3.68	1.43	–	–
523314	23314	8.0	CMC	+52/+49	0/5	3.77/3.68	1.02	–	–
44690	1039	7.5	CMC	+34/+60	0/5	3.72/4.47	0.83	–	–
80087	30053	200	PO	−9/+26	0/5	2.45/2.70	0.91	–	–
—	16866	30	CMC	+31/+48	2/10	3.01/4.43	0.68	±	–
525020	25020	500	CMC	+22/+34	2/5	3.55/2.56	1.39	–	–
2190	382	2500	S*	+44/+36	0/5	2.65/2.91	0.91	–	–
2190	382	1500	S*	+45/+43	1/10	2.93/3.26	0.90	–	–
2190	382	1250	S*	+31/+30	0/20	3.82/3.20	1.19	–	–
2190	382	250	S*	+40/+45	2/15	4.26/4.07	1.05	–	–
3060	420	8.0	S	+47/+51	1/5	5.20/4.71	1.10	–	–
—	3589	300	S	+18/+40	0/5	3.04/3.84	0.79	–	–
86016	9980	10	S	+37/+57	0/5	2.35/2.98	0.79	–	–
92859	29831	20	S	+21/+38	1/10	2.78/3.23	0.86	–	–

TABLE 9.—Effect of compounds on Murphy-Sturm lymphosarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
—	29857	250	S	+27/+35	1/10	3.10/3.76	0.82	–	–
3070	2800	5.0	CMC	+6/+39	1/5	3.53/4.07	0.87	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 10.—Effect of compounds on fibrosarcoma No. 1

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
23909	24464	20	S*	+14/+51	0/10	1.98/2.33	0.81	–	–
409962	27702	8.0	S*	0/+47	0/15	0.08/2.19	0.04	++	+++
409962	27702	4.0	S*	+15/+49	0/10	0.44/1.83	0.24	++	+
409962	27702	2.0	S*	+26/+44	0/5	1.14/1.77	0.64	±	–
409962	27702	1.0	S*	+36/+44	0/5	1.37/1.77	0.77	–	–
26271	20501	25	S*	+9/+43	0/15	0.19/3.47	0.05	++	++
9706	1133	0.25	S*	+26/+46	0/5	0.95/1.52	0.62	±	–
528988	28988	10	CMC	+29/+46	2/10	0.78/2.21	0.35	+	–
				II. Pyrimidine Analogs					
19893	18143	.25	S	+41/+40	0/5	1.29/1.60	0.81	–	–
				III. Purines and Analogs					
110037	17359	50	CMC	+49/+48	0/10	1.88/1.87	1.01	–	–
527612	27612	10	CMC	+37/+46	0/5	2.54/2.21	1.15	–	–
528403	28403	35	A+C	+41/+34	0/10	1.38/1.51	0.91	–	–
—	29830	35	CMC	+29/+47	0/10	0.86/2.58	0.33	+	–
—	30002	62.5	CMC	+6/+51	2/5	1.47/2.62	0.56	±	–
755	5357	30	CMC	−7/+35	3/15	1.23/2.00	0.62	±	–
528013+	28013	250	S	−8/+42	1/10	1.52/3.10	0.49	+	±
529509	29509	100	CMC	+44/+35	0/5	2.02/1.87	1.08	–	–
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+20/+51	2/10	0.72/1.90	0.38	+	±
				V. Steroids					
49420E	2795	37.5	CMC	+9/+41	0/5	1.48/1.52	0.97	–	–
9166E	2799	500	CMC	+31/+42	1/10	1.53/1.76	0.87	–	–
				VI. Antibiotics					
26980	19256	1.0	S	−3/+44	1/10	0.50/2.30	0.22	++	+
—	20779	2.0	S	+39/+43	0/10	2.89/2.98	0.97	–	–
—	30133	2.5	CMC	+28/+28	0/5	3.08/3.85	0.80	–	–
				VII. Quinolines					
529105	29105	15	CMC	+37/+35	0/5	1.91/2.60	0.73	±	–
529103	29103	2.0	CMC	+29/+36	0/5	2.26/2.59	0.87	–	–
529104	29104	25	CMC	+23/+36	0/5	2.52/2.59	0.97	–	–

TABLE 10.—Effects of compounds on fibrosarcoma No. 1—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				VIII. Miscellaneous Compounds					
67574	26327	0.125	S	+29/+49	0/5	2.66/3.18	0.84	−	−
—	28239	50	A+S	−10/+45	2/10	0.68/2.07	0.33	+	±
—	20497	250	S	+19/+41	0/5	2.06/2.41	0.85	−	−
109229	30000	5,000IU	S	+36/+68	0/10	2.43/3.94	0.62	±	−
109229	30000	1,667IU	S	+138/+161	0/5	6.40/5.95	1.08	−	−
109229	30000	167IU	S	+64/+68	0/10	2.52/4.06	0.62	±	−
32065	22591	200	CMC	+31/+41	0/5	1.47/2.41	0.61	±	−
80087	30053	200	PO	+40/+37	0/5	2.39/3.78	0.63	±	−
—	3589	300	S	+9/+41	0/5	1.92/2.41	0.80	−	−
—	3589	200	S	+57/+65	0/5	2.59/2.05	1.26	−	−
86016	9980	10	S	+46/+41	0/5	2.90/2.81	1.03	−	−
92859	29831	20	S	+13/+36	2/5	3.01/2.96	1.02	−	−
—	29857	250	S	+37/+38	2/10	2.21/2.68	0.82	−	−

*Compound solution or suspension prepared fresh daily.

TABLE 11.—Effect of compounds on fibrosarcoma No. 4

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
23909	24464	20	S*	+2/+44	0/5	0.91/1.22	0.75	±	−
409962	27702	8.0	S*	−7/+44	0/10	0.38/1.15	0.34	+	±
409962	27702	4.0	S*	+4/+38	0/5	0.60/1.00	0.60	±	−
409962	27702	2.0	S*	+21/+38	0/5	0.88/1.00	0.88	−	−
26271	20501	25	S*	+21/+47	0/10	0.28/1.08	0.26	+	+
9706	1133	0.25	S*	+25/+44	0/10	0.36/1.04	0.35	+	++
				II. Pyrimidine Analogs					
19893	18143	25	S	+40/+57	0/10	0.38/1.07	0.36	+	±
				III. Purines and Analogs					
110037	17359	50	CMC	+36/+45	0/5	0.69/1.14	0.60	±	−
527612	27612	10	CMC	+42/+45	0/5	1.04/1.14	0.91	−	−
528403	28403	70	A+C	+26/+47	0/5	0.51/2.08	0.25	++	+
528403	28403	35	A+C	+35/+45	0/15	0.35/1.21	0.29	+	+
755	5357	30	CMC	+8/+53	0/10	0.83/1.71	0.49	+	−
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+40/+41	2/10	0.19/1.03	0.18	++	+
				V. Steroids					
49420E	2795	37.5	CMC	+14/+52	0/5	0.93.1.71	0.54	±	−
9166E	2799	500	CMC	+53/+41	0/5	0.53/1.03	0.51	±	−
				VI. Antibiotics					
26980	19256	1.0	S	+3/+47	0/5	0.57/1.08	0.53	±	−

*Compound solution or suspension prepared fresh daily.

TABLE 12.—Effect of compounds on fibrosarcoma No. 6

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
23909	24464	20	S*	+15/+42	0/10	0.19/1.79	0.11	++	++
409962	27702	8.0	S*	−2/+37	0/10	0.04/1.47	0.03	++	+++
409962	27702	4.0	S*	+8/+31	0/10	0.0/1.20	0.0	+++	+++
26271	20501	50	S*	+7/+38	1/5	0.0/1.83	0.0	+++	+++
26271	20501	25	S*	+5/+38	0/10	0.0/2.22	0.0	+++	+++
9706	1133	0.25	S*	+35/+44	0/10	0.0/2.04	0.0	+++	+++
				II. Pyrimidine Analogs					
19893	18143	25	S	+35/+55	0/10	0.18/1.46	0.12	++	++
				III. Purines and Analogs					
—	17359	50	CMC	+34/+55	0/5	2.04/1.80	1.13	−	−
527612	27612	10	CMC	+38/+55	0/5	1.83/1.80	1.02	−	−
528403	28403	35	A+C	+41/+55	0/5	1.47/1.80	0.82	−	−
755	5357	30	CMC	−11/+43	1/5	0.45/1.36	0.33	+	±
528013+	28013	250	S	−5/+43	0/10	0.95/2.24	0.42	+	+
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+17/+43	1/10	0.09/1.56	0.06	++	+++
				V. Steroids					
49420E	2795	37.5	CMC	+7/+43	0/10	0.57/1.36	0.42	+	−
9166E	2799	500	CMC	+35/+58	0/5	1.61/1.78	0.90	−	−
				VI. Antibiotics					
26980	19256	1:0	S	−10/+49	0/10	0.07/1.49	0.05	++	++
—	20779	2.0	S	+39/+43	0/5	0.74/2.24	0.33	+	−
				VII. Miscellaneous Compounds					
—	20497	250	S	+19/+51	1/5	1.35/1.64	0.82	−	−
32065	22591	200	CMC	+42/+51	0/5	1.08/1.64	0.66	±	−
—	3589	300	S	+31/+46	4/10	1.49/1.77	0.84	−	−
—	3589	200	S	+43/+35	1/5	1.25/1.58	0.79	−	−
92859	29831	20	S	+39/+55	0/10	1.12/1.79	0.63	±	−

*Compound solution or suspension prepared fresh daily.

TABLE 13.—Effect of compounds on fibrosarcoma No. 7

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
23909	24464	20	S*	+6/+50	0/10	1.22/2.08	0.59	±	−
409962	27702	8.0	S*	−3/+51	0/10	0.0/2.31	0.0	+++	+++
409962	27702	4.0	S*	+15/+15	0/10	0.0/1.76	0.0	+++	+++
409962	27702	2.0	S*	+20/+37	1/5	0.0/1.59	0.0	+++	+++
409962	27702	1.0	S*	+25/+68	0/5	2.49/2.24	1.11	−	−
26271	20501	25	S*	+10/+42	0/10	0.0/2.13	0.0	+++	+++
9706	1133	0.25	S*	+17/+59	0/10	1.00/2.06	0.49	+	±

TABLE 13.—Effect of compounds on fibrosarcoma No. 7—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				II. Pyrimidine Analogs					
19893	18143	25	S	+27/+32	0/10	0.13/1.66	0.08	++	++
				III. Purines and Analogs					
—	17359	50	CMC	+35/+43	0/5	1.55/1.52	1.02	–	–
527612	27612	10	CMC	+46/+43	0/5	1.11/1.52	0.73	±	–
528403	28403	35	A+C	+52/+43	0/5	1.60/1.52	1.05	–	–
—	29830	35	CMC	+39/+51	0/5	2.20/2.50	0.88	–	–
755	5357	30	CMC	+3/+48	1/10	0.46/1.07	0.43	+	–
528013+	28013	250	S	−9/+34	0/5	1.30/2.65	0.49	+	±
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+35/+42	2/5	2.38/1.90	1.25	–	–
				V. Steroids					
49420E	2795	37.5	CMC	+13/+48	0/5	0.80/1.07	0.75	±	–
9166E	2799	500	CMC	+35/+41	0/15	1.17/1.63	1.10	–	–
				VI. Antibiotics					
26980	19256	1.0	S	+8/+47	0/5	0.05/2.67	0.02	++	++
26980	19256	0.5	S	+12/+41	0/10	0.21/1.27	0.17	++	+
—	20779	2.0	S	+37/+35	0/5	2.46/2.71	0.91	–	–
				VII. Miscellaneous Compounds					
67574	26327	0.125	S	+20/+61	0/5	1.87/2.02	0.93	–	–
32065	22591	200	CMC	+45/+48	0/5	0.81/1.19	0.68	±	–
—	3589	200	S	+41/+72	0/10	1.51/3.35	0.45	+	–
92859	29831	20	S	+20/+33	1/10	0.81/2.03	0.40	+	–

*Compound solution or suspension prepared fresh daily.

TABLE 14.—Effect of compounds on Babcock kidney tumor

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	0.25	S*	+15/+53	0/5	1.07/1.48	0.72	±	–
8806	15673	1.0	S*	+32/+51	1/15	1.79/2.09	0.81	–	–
525691	25691	12.5	CMC	+14/+49	0/5	1.60/1.84	0.87	–	–
526407	26407	25	CMC*	+14/+47	1/20	1.65/2.32	0.71	±	–
525823	25823	50	CMC*	−2/+47	0/10	1.43/1.91	0.75	±	–
526622	26622	250	CMC*	−5/+28	4/10	0.91/1.94	0.47	+	±
525022	25022	200	CMC*	−6/+53	2/15	0.84/2.20	0.38	+	±
526406	26406	25	CMC*	−7/+43	2/10	1.64/2.84	0.58	±	–
527453	27453	50	CMC*	+4/+36	0/15	1.03/1.27	0.81	–	–
62403	27456	2.0	CMC*	−1/+47	2/10	1.34/2.16	0.62	±	–
62403	27456	1.0	CMC*	+1/+46	0/10	1.53/1.48	1.03	–	–
62403	27456	0.5	CMC*	+43/+46	0/10	1.45/1.72	0.84	–	–
23909	24464	20	S*	+17/+52	0/10	0.46/1.55	0.30	+	±

TABLE 14.—Effect of compounds on Babcock kidney tumor—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
409962	27702	8.0	S*	−9/+43	0/15	0.68/2.05	0.33	+	±
47774	24591	25	CMC*	+41/+48	2/15	1.50/1.51	0.99	−	−
47774	24591	15	CMC*	+31/+38	0/5	1.51/2.15	0.70	±	−
750	5681	5.0	PO	+30/+49	0/5	2.20/2.46	0.89	−	−
3052	7505	50	PO	+18/+60	0/5	1.86/1.94	0.96	−	−
26271	20501	25	S*	+1/+43	1/15	0.76/1.62	0.47	+	±
26271	20501	12.5	S*	+28/+54	1/10	1.73/1.90	0.91	−	−
6396	6882	2.0	S*	+27/+53	2/5	1.75/1.48	1.18	−	−
				II. Pyrimidine Analogs					
19893	18143	25	S	+11/+49	0/25	1.35/2.13	0.63	±	−
27640	19150	40	S	+26/+43	2/20	1.86/2.29	0.81	−	−
				III. Purines and Analogs					
110037	17359	50	CMC	+34/+77	0/5	1.04/1.54	0.68	±	−
527612	27612	10	CMC	+34/+38	0/5	1.52/1.56	0.97	−	−
528403	28403	35	A+C	+41/+31	0/5	1.56/1.77	0.89	−	−
526485	26485	60	PO	+22/+47	1/10	0.60/1.43	0.42	+	−
755	5357	30	CMC	+5/+51	3/15	1.64/2.35	0.70	±	−
528013	28013	250	S	+42/+43	0/10	0.53/1.06	0.50	+	±
520950	20950	50	PO	+9/+41	0/5	1.69/1.76	0.96	−	−
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+22/+43	2/5	1.30/2.03	0.64	±	−
				V. Steroids					
49420E	2795	37.5	CMC	+9/+48	0/25	1.79/2.28	0.79	−	−
10483E	3047	37.5	CMC	−10/+46	1/5	1.30/2.49	0.52	±	−
9166E	2799	500	CMC	+54/+60	0/5	1.58/1.94	0.81	−	−
20293E	10696	40	CMC	+12/+60	0/5	1.98/1.94	1.02	−	−
				VI. Antibiotics					
185	903	0.25	S	+36/+52	0/15	1.04/1.73	0.60	±	−
3053	14095	0.025	A+S	+34/+41	2/10	1.15/1.47	0.78	−	−
58368	13617	50	CMC*	+35/+38	0/5	2.07/2.52	0.82	−	−
26980	19256	1.0	S	−10/+62	0/15	0.72/1.58	0.46	+	±
26980	19256	0.5	S	−5/+60	0/5	1.26/3.32	0.38	+	−
—	20779	4.0	S	−10/+30	2/10	0.66/2.30	0.29	+	±
—	20779	2.0	S	+28/+33	0/5	1.68/1.53	1.10	−	−
524678	24678	1.0	S	+23/+42	0/5	1.86/1.76	1.06	−	−
64393	14155	125	S	+44/+44	0/5	1.63/1.61	1.01	−	−
58514	20863	0.05	S*	+5/+45	3/15	0.81/1.50	0.54	±	−
58856	25707	1.25	A+W	+35/+45	0/5	1.31/1.61	0.81	−	−
526417	26417	0.025	A+S	+19/+46	0/10	2.09/2.63	0.79	−	−
526094	26094	0.005	A+S	+27/+43	1/20	2.14/2.63	0.81	−	−
525822	25822	0.005	A+S	+27/+40	4/20	1.47/2.03	0.72	±	−
52947	27773	1.0	S*	+41/+44	0/5	1.44/1.61	0.89	−	−
59729	28430	0.5	S	−4/+45	1/10	1.76/2.85	0.62	±	−
31083	21721	1,000	S	+39/+55	0/10	1.24/2.02	0.61	±	−
526368	26368	1.0	CMC	+33/+38	0/5	3.23/3.15	1.03	−	−
526598	26598	0.25	CMC	+37/+46	3/20	1.94/2.38	0.82	−	−
56410	25021	0.375	S	+2/+43	3/10	0.86/2.03	0.42	+	−
56410	25021	0.15	S	+12/+49	0/5	1.71/1.84	0.93	−	−
—	30133	2.5	CMC	+22/+40	0/5	2.50/2.74	0.91	−	−

TABLE 14.—Effect of compounds on Babcock kidney tumor—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				VII. Miscellaneous Compounds					
9170	15025	20	S	+12/+59	2/5	1.65/1.94	0.85	–	–
525816	25816	50	S	+34/+51	0/5	2.14/2.59	0.83	–	–
67574	26327	0.125	S	+27/+60	0/5	1.41/2.56	0.55	±	–
59354	25627	500	CMC	+29/+46	0/5	1.52/2.25	0.68	±	–
59354	25627	250	CMC	+12/+57	0/5	1.17/1.60	0.73	±	–
525602	25602	12.5	S	+51/+48	1/20	1.64/1.83	0.90	–	–
527516	27516	25	CMC	+23/+34	2/5	1.55/1.42	1.09	–	–
66248	26071	100	CMC*	+48/+46	0/5	1.74/2.25	0.77	–	–
49403	25112	62.5	CMC	+29/+43	0/5	3.24/3.58	0.91	–	–
23306	26081	60	CMC*	+32/+38	0/5	2.56/3.15	0.81	–	–
527517	27517	10	CMC	+20/+34	1/5	1.78/1.42	1.25	–	–
522600	22600	30	CMC	+39/+46	1/20	1.06/1.13	0.94	–	–
54186	24580	25	S*	+41/+47	0/15	1.96/2.04	0.96	–	–
524784	24784	1.0	S	+30/+35	0/5	0.71/1.19	0.60	±	–
—	20497	250	S	+5/+54	0/5	1.47/2.49	0.59	±	–
35843	24759	125	S	+16/+35	0/5	1.29/1.19	1.08	–	–
35847	24760	16	CMC	−6/+45	1/20	1.77/2.11	0.84	–	–
38280	24761	16	S	+26/+36	0/10	1.16/1.71	0.68	±	–
3051	8328	150	S	+14/+50	0/5	1.36/2.02	0.67	±	–
3051	8328	125	S	+26/+58	1/15	2.34/2.29	1.02	–	–
32065	22591	200	CMC	+32/+47	0/5	1.10/1.64	0.67	±	–
746	129	500	S	+30/+56	0/10	1.43/1.83	0.78	–	–
526741	26741	31.25	PO	+39/+51	1/5	1.36/1.51	0.90	–	–
526739	26739	500	PO	+54/+52	0/5	2.26/2.13	1.06	–	–
—	26744	15	PO	+37/+52	1/5	1.84/2.13	0.86	–	–
—	3589	200	S	+49/+70	0/5	1.12/1.74	0.64	±	–
86016	9980	10	S	+44/+51	0/5	2.30/2.29	1.00	–	–
92859	29831	20	S	+28/+44	0/10	0.36/1.26	0.29	+	±

*Compound solution or suspension prepared fresh daily.

TABLE 15.—Effect of compounds on Novikoff hepatoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	0.25	S*	+35/+34	0/5	2.65/2.23	1.19	–	–
8806	15673	1.0	S*	+27/+41	1/15	1.67/2.12	0.79	–	–
525691	25691	12.5	CMC	+39/+34	2/5	1.12/1.39	0.81	–	–
526407	26407	25	CMC*	+25/+39	0/10	1.30/1.36	0.96	–	–
525823	25823	50	CMC*	+33/+34	1/5	1.38/1.39	0.99	–	–
526622	26622	125	CMC*	−7/+55	0/10	1.71/1.51	1.13	–	–
525022	25022	200	CMC*	−10/+39	0/10	1.57/2.54	0.62	±	–
526406	26406	25	CMC*	+8/+51	2/15	1.41/2.84	0.50	+	±
750	5681	5.0	PO	+38/+38	0/5	1.97/1.73	1.14	–	–
3052	7505	50	PO	+32/+35	0/5	2.38/2.48	0.96	–	–
26271	20501	25	S*	+1/+41	2/15	1.00/2.50	0.40	+	–
9706	1133	0.125	S*	+40/+63	0/5	2.22/2.23	1.00	–	–

TABLE 15.—Effect of compounds on Novikoff hepatoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				II. Pyrimidine Analogs					
19893	18143	25	S	+5/+38	1/10	1.84/1.73	1.06	–	–
27640	19150	40	S	+23/+34	0/5	2.62/2.25	1.16	–	–
				III. Purines and Analogs					
526485	26485	60	PO	+20/+56	1/10	1.36/1.65	0.82	–	–
755	5357	30	CMC	+44/+34	0/10	2.94/2.75	1.07	–	–
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+15/+38	2/5	1.90/1.73	1.10	–	–
—	24813	30	CMC	+24/+47	0/10	0.55/1.34	0.41	+	–
				V. Steroids					
49420E	2795	37.5	CMC	+3/+34	2/5	3.10/2.25	1.38	–	–
20293E	10696	40	CMC	+13/+46	1/15	1.14/1.93	0.59	±	–
				VI. Antibiotics					
185	903	0.25	S	+25/+47	0/5	0.90/1.34	0.67	±	–
3053	14095	0.025	A+S	+57/+63	2/5	3.13/2.23	1.40	–	–
26980	19256	1.0	S	−5/+53	2/15	1.11/1.89	0.59	±	–
58514	20863	0.025	S*	+40/+47	0/10	1.67/2.12	0.79	–	–
58856	25707	1.25	A+W	+39/+30	0/5	2.23/2.12	1.05	–	–
526417	26417	0.025	A+S	+28/+44	1/10	2.24/1.95	1.15	–	–
526094	26094	0.005	A+S	+52/+39	2/10	1.73/2.43	0.71	±	–
526094	26094	0.0025	A+S	+43/+44	0/5	4.16/3.68	1.13	–	–
525822	25822	0.005	A+S	+32/+40	2/15	1.40/1.85	0.76	–	–
525822	25822	0.0025	A+S	+23/+40	0/5	1.85/1.85	1.00	–	–
52947	27773	1.0	S*	+29/+34	0/5	1.33/1.39	0.96	–	–
526368	26368	1.0	CMC	+49/+32	0/5	3.18/2.64	1.20	–	–
526598	26598	0.25	CMC	+55/+44	1/5	4.98/3.68	1.34	–	–
				VII. Miscellaneous Compounds					
53582	25513	30	CMC*	+43/+49	0/15	1.29/1.72	0.75	±	–
49403	25512	125	CMC	+41/+39	0/5	2.55/2.42	1.05	–	–
23306	26081	60	CMC*	+5/+53	0/5	1.78/1.48	1.20	–	–
35847	24760	8.0	CMC	+20/+42	2/15	1.77/2.85	0.62	±	–
38280	24761	16	S	+32/+30	0/5	1.87/2.12	0.88	–	–
3051	8328	125	S	+42/+25	0/5	2.23/2.48	0.90	–	–
746	129	500	S	+30/+62	0/10	0.97/1.34	0.72	–	–
139	27091	30	CMC	+20/+50	0/10	1.65/1.38	1.19	–	–
526741	26741	125	PO	+18/+59	2/5	1.72/1.34	1.28	–	–
526739	26739	500	A+P	+51/+59	0/5	1.41/1.34	1.05	–	–
—	26744	15	PO	+43/+54	0/5	1.93/1.87	1.03	–	

*Compound solution or suspension prepared fresh daily.

TABLE 16.—Effect of compounds on Iglesias ovarian tumor

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of fourth week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 5 weeks
				I. Alkylating Agents					
762	101	0.125	S*	+47/+47	0/10	0.80/1.18	0.68	±	–
8806	15673	1.0	S*	+49/+48	0/5	0.58/1.77	0.33	+	–
—	20597	1.0	S*	+47/+48	0/10	0.79/1.77	0.45	+	–
525691	25691	12.5	CMC	+55/+35	4/10	0.50/1.00	0.50	+	–
526407	26407	25	CMC*	+35/+48	0/10	0.48/2.24	0.21	++	+
526406	26406	25	CMC*	+20/+38	1/5	0.05/1.73	0.03	++	++
527453	27453	50	CMC*	+27/+38	0/10	0.15/1.00	0.15	++	±
62403	27456	1.0	CMC*	+23/+55	6/15	0.86/2.39	0.36	+	±
62403	27456	0.5	CMC*	+26/+54	2/10	0.43/1.38	0.31	+	±
62403	27456	0.25	CMC*	+50/+62	1/10	0.62/1.08	0.57	±	±
23909	24464	20	S*	−15/+6	1/5	0.10/1.61	0.06	++	++
409962	27702	8.0	S*	+1/+21	0/10	0.0/1.23	0.0	+++	+++
47774	24591	25	CMC*	+11/+17	0/5	0.55/1.31	0.42	+	–
3052	7505	50	PO	+48/+55	0/10	0.51/2.64	0.19	++	+
3094	11687	50	PO	+18/+48	3/15	1.21/2.27	0.53	±	±
3094	11687	35	PO	+53/+26	1/5	2.54/1.85	1.37	–	–
3094	11687	25	PO	+39/+42	0/5	0.74/1.03	0.72	±	–
408428	14405	125	CMC	+19/+26	1/5	1.25/1.22	1.02	–	–
48821	15128	50	S	+30/+26	2/5	1.55/1.27	1.22	–	–
—	15749	250	PO	+13/+26	1/5	1.20/1.22	0.98	–	–
26271	20501	25	S*	0/+46	3/15	0.0/1.11	0.0	+++	+++
26271	20501	12.5	S*	−4/+45	0/5	0.0/2.15	0.0	+++	+++
26271	20501	6.25	S*	+13/+68	0/5	0.86/1.08	0.80	–	–
520644	20644	25	CMC*	+17/+53	2/5	0.05/1.38	0.04	++	++
520645	20645	50	CMC*	+36/+53	0/5	0.50/1.38	0.36	+	+
520645	20645	25	CMC*	+37/+33	2/5	2.10/1.91	1.10	–	–
520645	20645	12.5	CMC*	+24/+37	0/5	1.74/2.36	0.74	±	–
42158	17360	10	S*	+28/+46	0/10	0.09/1.30	0.07	++	±
9706	1133	0.25	S*	+63/+46	2/5	0.65/1.15	0.56	±	–
9706	1133	0.125	S*	+49/+45	2/15	0.70/1.20	0.58	±	–
				II. Pyrimidine Analogs					
19893	18143	25	S	+48/+73	0/5	2.10/2.84	0.74	±	–
19940	1507	250	CMC	+36/+33	0/5	1.39/1.91	0.73	±	–
27640	19150	40	S	+38/+57	2/10	2.08/2.03	1.02	–	–
48006	20000	10	S	−4/+39	3/10	010/1.91	0.05	++	++
				III. Purines and Analogs					
526485	26485	60	PO	+29/+56	0/5	1.36/1.93	0.70	±	–
755	5357	30	CMC	+42/+45	0/10	1.23/1.35	0.91	–	–
38887	20355	10	CMC	+35/+38	0/5	1.69/1.85	0.91	–	–
25650	14944	100	S	+33/+31	0/5	1.52/1.46	1.04	–	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+27/+64	3/10	0.83/2.18	0.38	+	±
1393	13148	10	CMC	+36/+33	0/5	0.79/1.53	0.52	±	–
740	1275	0.5	S*	+48/+35	1/5	1.31/1.01	1.30	–	–
				V. Steroids					
49420E	2795	37.5	CMC	+31/+43	0/10	1.41/1.68	0.84	–	–
10483E	2047	37.5	CMC	+8/+34	1/5	0.50/1.11	0.45	+	–
12600E	15347	3.0	CMC	+2/+33	2/5	1.08/1.53	0.71	±	–
12601E	18062	2.5	CMC	+18/+67	1/5	0.68/1.99	0.34	+	±

TABLE 16.—Effect of compounds on Iglesias ovarian tumor—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of fourth week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 5 weeks
9166E	2799	500	CMC	+33/+34	0/5	1.46/1.11	1.32	−	−
20293E	10696	40	CMC	+16/+91	1/5	2.90/2.46	1.18	−	−
17592	24924	500	PO	+38/+45	1/5	1.70/2.15	0.79	−	−
				VI. Antibiotics					
9169	2859	150	S	+25/+33	0/5	0.69/1.17	0.59	±	−
185	903	1.0	S	+32/+53	0/10	0.37/1.05	0.35	+	±
185	903	0.5	S	+5/+42	0/5	1.47/1.03	1.43	−	−
17257	17442	1.0	S	+42/+38	2/5	2.85/2.76	1.03	−	−
3067	2662	7.5	CMC	+21/+45	0/5	0.96/1.10	0.87	−	−
9168	6258	10	CMC	+46/+79	2/10	1.50/2.23	0.67	±	−
9168	6258	5.0	CMC	+14/+33	1/5	0.85/1.17	0.73	±	−
3053	14095	0.025	A+S	+20/+36	0/10	0.84/1.54	0.55	±	−
—	16701	0.025	S	+69/+53	0/5	1.38/1.38	1.00	−	−
26980	19256	1.0	S	−9/+31	1/10	0.0/1.46	0.0	+++	+++
26980	19256	0.5	S	+16/+40	0/5	0.22/1.22	0.18	++	+
—	28145	2.5	A+S	+18/+48	0/5	0.74/1.58	0.47	+	−
—	28242	2.5	A+S	+27/+31	0/10	0.56/1.83	0.31	+	−
524678	24678	0.5	S	+30/+31	1/5	1.58/1.32	1.20	−	−
58514	20863	0.05	S*	+29/+35	2/5	0.95/2.50	0.38	+	±
58514	20863	0.025	S*	+49/+39	1/10	0.92/1.96	0.47	+	±
58856	25707	1.25	A+W	+52/+24	0/5	0.90/1.62	0.56	±	−
526417	26417	0.0125	A+S	+27/+44	3/10	1.11/2.24	0.50	+	−
52947	27773	1.0	S*	+35/+66	0/5	1.88/2.22	0.85	−	−
59729	28430	0.25	S	+38/+38	0/5	1.12/1.78	0.63	±	−
83340	28487	5.0	S	+28/+37	0/10	0.13/1.22	0.11	++	++
39147	20250	0.15	S	+29/+38	0/5	0.80/1.85	0.43	+	−
45383	20556	0.1	A+S	+25/+38	2/10	0.28/2.76	0.10	++	++
53104	21568	500	CMC	+19/+33	1/5	0.70/1.17	0.60	±	−
31083	21721	500	S	+62/+59	0/5	0.34/1.12	0.30	+	±
526368	26368	1.0	CMC	+45/+55	2/5	2.72/2.48	1.10	−	−
526598	26598	0.5	CMC	+61/+45	2/5	3.25/2.30	1.41	−	−
56410	25021	0.182	S	+21/+37	1/5	0.43/1.03	0.42	+	±
				VII. Miscellaneous Compounds					
9170	15025	10	S	+36/+39	2/5	1.55/1.22	1.27	−	−
—	21509	250	S	+49/+30	0/5	1.81/1.51	1.20	−	−
4	3844	50	CMC	+38/+31	0/5	1.37/1.46	0.94	−	−
14574	1471	50	S	+39/+34	0/5	0.42/1.11	0.38	+	−
59354	25627	250	CMC	+20/+37	0/5	0.63/1.03	0.61	±	−
5354	1147	200	S*	+22/+35	0/5	0.68/1.01	0.67	±	−
525602	25602	12.5	S	+50/+39	0/5	0.70/1.00	0.70	±	−
525442	25442	125	CMC	+50/+38	1/5	0.71/1.00	0.71	±	−
53582	25513	31.3	CMC*	+32/+38	0/10	0.10/1.78	0.06	++	+
49403	25512	125	CMC	+27/+41	2/5	0.01/1.11	0.0	+++	+++
49403	25512	62.5	CMC	+54/+49	2/15	0.84/1.89	0.44	+	−
23306	26081	60	CMC*	+28/+40	1/5	1.33/1.11	1.20	−	−
522600	22600	30	CMC	+51/+57	4/10	1.29/2.84	0.45	+	±
24854	20895	1000	S	+27/+52	1/10	1.18/1.63	0.72	±	−
54186	24580	25	S*	+33/+56	1/10	1.22/1.70	0.72	±	−
—	20845	25	S	+37/+33	2/5	2.10/1.91	1.10	−	−
35843	24759	125	S	+17/+59	0/5	0.46/1.03	0.45	+	−
3051	8328	62.5	S	+47/+42	2/5	0.85/1.03	0.83	−	−
526739	26739	500	A+P	+14/+30	0/5	1.17/1.38	0.85	−	−

TABLE 16.—Effect of compounds on Iglesias ovarian tumor—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of fourth week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 5 weeks
—	127	500	CMC	+35/+53	0/5	0.86/1.05	0.82	–	–
3070	2800	10	CMC	+67/+65	1/5	3.91/3.22	1.21	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 17.—Effect of compounds on Iglesias sarcoma

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
				I. Alkylating Agents					
762	101	0.5	S*	0/+45	1/10	2.01/3.83	0.52	±	–
8806	15673	1.0	S*	+10/+30	2/25	0.65/3.59	0.18	++	±
525691	25691	12.5	CMC	+8/+32	1/15	0.19/3.50	0.26	+	±
526407	26407	25	CMC*	−3/+26	3/10	0.38/3.85	0.10	++	+
525823	25823	200	CMC*	−11/+40	0/10	0.05/3.12	0.02	++	++
525823	25823	100	CMC*	−8/+10	0/10	0.70/4.08	0.17	++	±
525823	25823	50	CMC*	+1/+25	0/5	1.89/3.58	0.53	±	–
526622	26622	250	CMC*	−10/+24	2/10	0.28/4.01	0.07	++	++
526622	26622	125	CMC*	0/+23	1/5	0.86/3.60	0.24	++	++
525022	25022	200	CMC*	−16/+34	1/10	0.14/3.09	0.05	++	++
526406	26406	25	CMC*	−4/+26	2/10	0.30/3.47	0.09	++	++
527453	27453	50	CMC*	+9/+29	0/10	0.26/2.89	0.09	++	+
62403	27456	1.0	CMC*	−8/+33	8/25	1.30/3.43	0.38	+	±
47774	24591	25	CMC*	0/+20	0/5	3.09/3.91	0.79	–	–
3094	11687	50	PO	−6/+37	1/5	3.11/4.10	0.76	–	–
26271	20501	25	S*	−5/+34	2/20	0.61/3.78	0.16	++	+++
26271	20,501	12.5	S*	0/+18	2/10	0.65/3.55	0.18	++	++
26271	20501	6.25	S*	+5/+7	0/10	0.40/1.94	0.21	++	++
520645	20645	50	CMC*	+26/+47	0/5	3.41/4.42	0.77	–	–
42158	17360	40	S*	+39/+35	0/5	0.56/2.32	0.24	++	±
42158	17360	20	S*	+33/+24	0/10	1.24/3.42	0.36	+	±
9706	1133	0.125	S*	+12/+41	0/10	2.44/4.05	0.60	±	–
				II. Pyrimidine Analogs					
146604	19273	5.0	S	+33/+16	2/5	2.86/3.66	0.78	–	–
27640	19150	40	S	+27/+45	0/5	2.99/3.89	0.77	–	–
48006	20000	5.0	S	+7/+5	2/5	2.12/3.34	0.63	±	–
				III. Purines and Analogs					
755	5357	30	CMC	+36/+36	0/5	3.31/3.70	0.89	–	–
520950	20950	50	PO	+8/+30	0/5	3.02/4.00	0.76	–	–
				IV. Antimetabolites and Folic Acids					
742	9505	2.5	S*	+16/+24	0/5	3.76/4.21	0.89	–	–
				V. Steroids					
49420E	2795	37.5	CMC	−7/+33	0/5	2.49/3.99	0.62	±	–
10483E	3047	37.5	CMC	−4/+32	0/10	1.60/4.03	0.40	+	–
10483E	3047	18.75	CMC	+26/+16	1/5	4.02/3.66	1.10	–	–

TABLE 17.—Effect of compounds on Iglesias sarcoma—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 3 weeks
9166E	2799	500	CMC	+31/+38	1/5	3.41/3.73	0.91	–	–
20293E	10696	40	CMC	+16/+28	0/5	3.18/3.80	0.84	–	–
17592	24924	500	PO	+19/+30	0/5	3.69/4.17	0.88	–	–
				VI. Antibiotics					
185	903	1.0	S	+9/+45	2/5	2.95/4.24	0.70	±	–
3053	14095	0.025	A+S	+25/+32	0/5	3.88/4.03	0.96	–	–
26980	19256	1.0	S	−7/+31	3/10	0.30/3.93	0.08	++	+
26980	19256	0.5	S	+20/+36	0/10	2.72/4.29	0.63	±	–
26980	19256	0.25	S	+46/+36	0/5	4.27/4.15	1.03	–	–
524678	24678	1.0	S	+4/+17	2/10	2.93/3.57	0.82	–	–
58514	20863	0.05	S*	+28/+42	1/5	3.15/3.09	1.02	–	–
58514	20863	0.025	S*	+38/+53	0/5	4.44/3.64	1.22	–	–
58856	25707	0.625	A+W	+26/+21	0/5	4.04/3.51	1.15	–	–
526417	26417	0.025	A+S	+17/+36	1/10	3.22/4.07	0.79	–	–
526094	26094	0.005	A+S	+21/+29	1/5	4.04/4.09	0.99	–	–
525822	25822	0.005	A+S	+25/+23	0/5	3.90/3.54	1.10	–	–
52947	27773	1.0	S*	+19/+30	1/5	4.10/4.00	1.03	–	–
59729	28430	0.25	S	+1/+30	2/10	3.06/4.20	0.73	±	–
51812	24907	40	CMC*	+9.0/+22	0/5	3.49/3.78	0.92	–	–
526598	26598	0.5	CMC	+23/+41	0.5	3.91/4.19	0.93	–	–
56410	25021	0.375	S	+4/+43	1/10	2.93/4.26	0.69	±	–
				VII. Miscellaneous Compounds					
14574	1471	50	S	+9/+32	0/5	3.00/4.03	0.74	±	–
59354	25627	250	CMC	+24/+28	0/5	3.94/4.28	0.92	–	–
5354	1147	200	S*	+23/+38	0/5	3.21/3.73	0.86	–	–
525602	25602	12.5	S	+30/+10	0/5	4.08/4.08	1.00	–	–
527516	27516	25	CMC	−10/+53	2/5	3.08/3.64	0.85	–	–
66248	26071	100	CMC*	+9/+30	1/10	2.75/3.92	0.70	±	–
23306	26081	60	CMC	+25/+22	0/5	3.57/4.54	0.79	–	–
527517	27517	10	CMC	+18/+44	2/5	3.58/4.35	0.82	–	–
24854	20895	1000	S	−8/+30	1/5	3.10/4.13	0.75	±	–
54186	24580	25	S*	+18/+30	0/5	3.64/4.13	0.88	–	–
35847	24760	16	CMC	+8/+23	1/10	3.70/3.54	1.05	–	–
38280	24761	16	S	+13/+21	0/5	3.68/3.51	1.05	–	–
746	129	500	S	+25/+45	0/5	3.33/4.24	0.79	–	–
526741	26741	62.5	PO	+50/+45	2/5	4.00/3.15	1.27	–	–
526739	26739	500	A+P	+32/+24	0/5	4.26/4.88	0.87	–	–
—	26744	15	PO	+41/+45	1/5	3.60/3.15	1.14	–	–
523316	23316	20	CMC	+38/+23	1/5	3.97/3.65	1.09	–	–
523314	23314	8.0	CMC	+32/+23	0/5	3.96/3.65	1.08	–	–
526318	26318	1.0	CMC	+28/+22	0/5	4.39/4.54	0.97	–	–

*Compound solution or suspension prepared fresh daily.

TABLE 18.—Effect of compounds on Iglesias adrenal tumor

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of eighth week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 9 weeks
				I. Alkylating Agents					
762	101	0.25	S*	+88/+102	0/10	0.93/1.10	0.85	−	−
762	101	0.125	S*	+163/+136	0/5	1.50/1.30	1.15	−	−
8806	15673	2.0	S*	+100/+77	0/5	0.44/1.20	0.37	+	±
8806	15673	1.0	S*	+73/+126	0/5	0.99/1.00	0.99	−	−
525691	25691	25	CMC	+45/+43	1/5	0.25/1.00	0.25	++	+
525691	25691	6.25	CMC	+108/+115	0/5	1.37/1.05	1.30	−	−
526407	26407	25	CMC*	+65/+69	1/5	0.76/1.01	0.75	±	−
525823	25823	200	CMC*	+33/+78	2/5	0.48/1.00	0.48	+	−
525022	25022	100	CMC*	+78/+105	2/10	0.96/1.16	0.83	−	−
526406	26406	25	CMC*	+71/+115	1/5	0.95/1.05	0.90	−	−
527453	27453	50	CMC*	+69/+96	3/10	0.05/1.17	0.04	++	++
62403	27456	1.0	CMC*	+78/+94	3/10	0.12/1.31	0.09	++	++
62403	27456	0.5	CMC*	+82/+77	2/15	0.40/1.20	0.33	+	±
62403	27456	0.25	CMC*	+100/+93	2/10	0.89/1.03	0.86	−	−
23909	24464	20	S*	+45/+76	2/5	0.43/1.30	0.33	+	+
409962	27702	8.0	S*	−6/+93	2/10	0.0/1.04	0.0	+++	+++
47774	24591	15	CMC*	+88/+69	2/5	0.58/1.04	0.56	±	−
3052	7505	50	PO	+92/+99	2/15	0.56/1.60	0.35	+	±
3094	11687	50	PO	+48/+118	1/10	0.98/1.04	0.94	−	−
26271	20501	6.25	S*	+41/+43	1/5	0.66/1.00	0.66	±	−
520645	20645	50	CMC*	+64/+98	0/5	1.22/1.15	1.06	−	−
42158	17360	20	S*	+53/+104	0/5	1.12/1.00	1.12	−	−
9706	1133	0.25	S*	+106/+136	0/5	0.92/1.30	0.71	±	−
9706	1133	0.125	S*	+102/+116	0/5	1.16/1.66	0.70	±	−
				II. Pyrimidine Analogs					
19940	1507	250	CMC	+123/+98	0/5	1.84/1.27	1.45	−	−
				III. Purines and Analogs					
755	5357	30	CMC	+101/+111	0/5	0.61/1.11	0.55	±	−
755	5357	15	CMC	+151/+136	0/5	0.90/1.30	0.69	±	−
58385	14377	10	CMC	+37/+36	0/5	1.22/1.46	0.84	−	−
				IV. Antimetabolites and Folic Acids					
740	1275	0.5	S*	+81/+99	2/5	0.88/1.09	0.81	−	−
				V. Steroids					
49420E	2795	37.5	CMC	+69/+81	0/10	0.89/1.21	0.74	±	−
49420E	2795	25	CMC	+156/+136	0/5	1.21/1.30	0.93	−	−
12601E	18062	2.5	CMC	+65/+120	2/5	1.67/1.35	1.24	−	−
				VI. Antibiotics					
185	903	1.0	S	+40/+116	1/5	0.82/1.66	0.49	+	±
3067	2662	15	CMC	+59/+77	0/5	0.79/1.20	0.66	±	−
9168	6258	5.0	CMC	+93/+73	0/5	0.90/1.67	0.54	±	−
18268	11822	0.025	A+S	+97/+80	0/5	0.96/1.25	0.77	−	−
3053	14095	0.025	A+S	+88/+90	0/10	1.38/1.09	1.27	−	−
—	16701	0.025	A+S	+85/+98	0/5	1.75/1.35	1.30	−	−
26980	19256	1.0	S	+38/+119	3/10	0.61/1.26	0.48	+	±
—	28242	2.5	A+S	+43/+43	2/10	0.10/1.02	0.10	++	+
524678	24678	0.25	S	+58/+157	0/5	0.98/1.08	0.91	−	−
58514	20863	0.025	S*	+58/+72	2/10	0.72/1.18	0.61	±	−
58856	25707	1.25	A+W	+60/+63	2/5	1.05/1.12	0.94	−	−

TABLE 18.—Effect of compounds on Iglesias adrenal tumor—Continued

NSC No.	SK No.	Dose (mg/kg/day)	Vehicle	Results at end of eighth week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results at 9 weeks
526417	26417	0.025	A+S	+123/+140	0/10	0.66/1.35	0.49	+	−
526094	26094	0.005	A+S	+78/+126	2/5	0.49/1.13	0.43	+	±
525822	25822	0.0025	A+S	+58/+52	0/5	0.95/1.14	0.83	−	−
52947	27773	1.0	S*	+94/+96	4/10	1.13/1.34	0.84	−	−
39147	20250	0.15	S	+100/+101	0/5	0.51/1.18	0.43	+	−
45383	20556	0.1	A+S	+33/+36	1/5	0.40/1.46	0.27	+	++
31083	21721	500	S	+114/+108	2/5	0.77/1.09	0.71	±	−
526368	26368	1.0	CMC	+117/+126	1/5	0.89/1.13	0.79	−	−
56410	25021	0.182	S	+87/+84	1/5	0.33/1.17	0.28	+	+
				VII. Miscellaneous Compounds					
—	21509	250	S	+109/+47	1/5	1.48/1.28	1.16	−	−
4	3844	50	CMC	+117/+139	0/5	1.28/1.25	1.02	−	−
59354	25627	250	CMC	+69/+68	3/10	0.57/2.40	0.24	++	+
527516	27516	12.5	CMC	+103/+93	1/5	0.79/1.16	0.68	±	−
527517	27517	10	CMC	+113/+140	2/5	0.53/1.19	0.45	+	±
24854	20895	250	S	+85/+89	1/15	0.83/1.16	0.72	±	−
54186	24580	12.5	S*	+70/+157	1/5	1.57/1.08	1.45	−	−
35843	24759	125	S	+13/+78	1/10	0.0/1.00	0.0	+++	+++
35847	24760	8.0	CMC	+29/+78	2/5	0.05/1.00	0.05	++	++
35847	24760	4.0	CMC	+92/+69	1/10	1.03/1.08	0.95	−	−
38280	24761	8.0	S	+111/+109	1/5	1.76/1.23	1.43	−	−
746	129	500	S	+67/+100	2/10	0.94/1.30	0.72	±	−
523316	23316	20	CMC	+62/+90	2/5	1.38/1.11	1.24	−	−
523316	23316	10	CMC	+59/+116	2/5	1.13/1.27	0.89	−	−
523314	23314	8.0	CMC	+65/+90	2/5	0.90/1.11	0.81	−	−
—	5490	250	S	+67/+52	0/5	0.75/1.14	0.66	±	−

*Compound solution or suspension prepared fresh daily.

TABLE 19.—Chemotherapy of well-established rat tumors (7-day-old)

NSC No.	SK No.	Tumor	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results on 1-day-old tumors
762	101	FRC	0.50	−8/+48	0/10	0.82/2.37	0.35	+	++
762	101	FRC	0.25	−9/+40	0/20	1.06/1.38	0.77	−	−
762	101	JRS	0.25	+7/+26	0/10	1.06/4.13	0.26	+	++
762	101	R39	0.50	−20/+32	2/20	1.79/2.94	0.61	±	++
762	101	R39	0.25	+4/+25	0/20	0.93/2.00	0.46	+	+
10107	598	FRC	1.5	−20/+31	0/30	0.65/1.73	0.38	+	+++
10107	598	W256	1.5	−3/+43	2/20	1.55/3.18	0.49	+	+
10107	598	JRS	1.5	+10/+30	0/20	0.22/2.49	0.09	++	+++
10107	598	MRLS	1.5	−19/+39	2/10	1.95/3.57	0.55	±	−
9506	1424	FRC	5.0	−15/+32	1/40	0.12/1.84	0.07	++	++
9506	1424	FRC	0.25	−5/+18	0/10	0.14/1.00	0.14	++	++
9506	1424	W256	5.0	−10/+43	0/20	1.16/2.40	0.48	+	++
9506	1424	W256	2.5	+8/+34	1/10	0.80/1.30	0.62	±	+
9506	1424	W256	1.0	+24/+34	0/10	0.81/1.30	0.62	±	±
9506	1424	JRS	5.0	−20/+40	1/10	0.38/2.90	0.13	++	++
9506	1424	R39	5.0	−12/+30	0/30	0.0/2.63	0.0	+++	++

TABLE 19.—Chemotherapy of well-established rat tumors (7-day-old)—Continued

NSC No.	SK No.	Tumor	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results on 1-day-old tumors
9506	1424	R39	2.5	−8/+50	0/10	0.55/4.44	0.12	++	++
9506	1424	R39	1.0	+24/+32	1/20	2.94/3.88	0.76	−	−
8806	15673	W256	1.0	+5/+37	1/10	1.10/2.65	0.42	+	++
8806	15673	JRS	1.0	+41/+66	2/30	0.65/3.05	0.21	++	++
8806	15673	YRS	1.0	+66/+77	0/10	0.0/2.61	0.0	+++	+++
525691	25691	JRS	12.5	+32/+68	0/20	0.14/4.60	0.03	++	++
525691	25691	YRS	12.5	+57/+76	0/10	0.0/3.28	0.0	+++	+++
525022	25022	W256	200	+20/+72	0/10	1.47/3.19	0.46	+	++
526406	26406	JRS	25	+6/+47	1/10	1.46/2.79	0.52	±	++
62403	27456	FRC	1.0	+55/+65	0/10	0.10/2.71	0.04	++	++
62403	27456	JRS	2.0	+1/+62	0/40	1.17/3.37	0.35	+	+++
62403	27456	JRS	1.0	+17/+57	0/30	1.39/2.92	0.48	+	++
62403	27456	YRS	2.0	−12/+83	0/10	0.0/1.87	0.0	+++	+++
409962	27702	FRC	8.0	+6/+62	1/20	0.22/2.78	0.08	++	+++
409962	27702	W256	8.0	+15/+82	0/20	2.38/4.42	0.54	±	++
409962	27702	JRS	8.0	+13/+72	0/20	0.44/3.95	0.11	++	+++
409962	27702	YRS	8.0	+6/+65	0/20	0.0/2.13	0.0	+++	+++
409962	27702	RFS No. 1	8.0	+2/+62	0/30	0.27/2.53	0.11	++	++
409962	27702	RFS No. 1	4.0	+32/+73	0/10	1.60/2.50	0.64	±	++
17016	6699	JRS	100	+3/+53	0/10	2.46/3.95	0.62	±	++
750	5681	W256	5.0	+21/+61	2/20	1.37/2.68	0.51	±	++
750	5681	JRS	10	−5/+17	1/10	1.57/4.36	0.36	+	
750	5681	JRS	5.0	+17/+46	5/30	1.88/3.25	0.58	±	±
3052	7505	FRC	50	+36/+45	0/20	0.58/1.80	0.32	+	++
3052	7505	W256	50	+15/+53	3/20	1.23/3.53	0.35	+	++
3052	7505	JRS	50	+23/+57	2/40	0.76/3.92	0.19	++	+++
49421	4614	FRC	2.5	+71/+58	0/10	0.59/2.55	0.23	++	
49421	4614	FRC	1.0	+44/+31	2/20	0.35/1.12	0.31	+	++
49421	4614	W256	1.0	+35/+57	3/30	2.15/3.72	0.58	±	++
49421	4614	JRS	1.0	+5/+54	4/20	1.00/3.47	0.29	+	++
49421	4614	R39	2.5	+30/+44	2/20	0.46/2.55	0.18	++	+++
49421	4614	R39	1.0	+18/+34	0/20	1.27/3.38	0.38	+	
49421	4614	MRLS	1.0	+22/+45	0/10	2.32/2.92	0.79	−	−
9717	3818	FRC	1.0	+24/+44	4/50	0.52/1.86	0.28	+	++
9717	3818	W256	2.5	−10/+18	1/10	1.71/3.31	0.52	±	
9717	3818	W256	1.0	+28/+52	2/50	1.62/3.36	0.48	+	++
9717	3818	JRS	1.0	+30/+48	3/50	0.86/3.77	0.23	++	+++
9717	3818	R39	1.0	+33/+52	0/20	0.34/2.73	0.12	++	+++
9717	3818	MRLS	1.0	+12/+26	0/20	4.00/3.87	1.03	−	−
26271	20501	FRC	25	+18/+63	7/40	0.45/1.86	0.24	++	++
26271	20501	FRC	12.5	+54/+87	2/20	0.19/1.68	0.11	++	++
26271	20501	W256	25	+24/+61	2/40	0.68/3.80	0.18	++	++
26271	20501	JRS	50	+8/+19	0/10	0.0/3.73	0.0	+++	+++
26271	20501	JRS	25	+6/+53	1/20	0.70/3.05	0.23	++	+++
26271	20501	JRS	12.5	+10/+55	2/20	0.0/2.67	0.0	+++	+++
26271	20501	MRS No. 1	25	+3/+57	2/20	0.89/2.17	0.41	+	+
26271	20501	MRLS	25	+6/+34	1/20	0.57/3.79	0.15	++	+
26271	20501	OT	25	+11/+30	0/10	3.04/4.00	0.76	−	+++
520644	20644	JRS	25	+20/+74	2/10	0.0/2.86	0.0	+++	+++
42158	17360	JRS	20	+41/+80	1/10	0.12/4.33	0.03	++	+++
—	2732	W256	500	+19/+43	0/10	2.74/3.93	0.70	±	++
9706	1133	FRC	0.5	+23/+31	0/20	0.38/2.33	0.16	++	++
9706	1133	FRC	0.25	+12/+32	1/50	0.57/1.99	0.29	+	++
9706	1133	W256	0.5	−30/+20	2/20	0.86/3.05	0.28	+	++
9706	1133	W256	0.25	−8/+38	0/40	1.78/3.16	0.56	±	++

TABLE 19.—Chemotherapy of well-established rat tumors (7-day-old)—Continued

NSC No.	SK No.	Tumor	Vehicle	Results at end of second week: Avg wt change (g) treated/control	No. of deaths	Avg tumor diam (cm) treated/control	Tumor index	Results of treatment	Results on 1-day-old tumors
9706	1133	JRS	0.25	+17/+58	0/20	1.20/2.74	0.44	+	++
9706	1133	R39	0.25	+5/+37	0/50	0.0/4.23	0.0	+++	+++
9706	1133	MRLS	0.25	−15/+25	0/20	2.20/3.64	0.60	±	−
6396	6882	FRC	2.0	+26/+57	1/40	0.29/2.00	0.15	++	+++
6396	6882	FRC	1.0	+54/+55	1/20	0.22/2.13	0.10	++	+++
6396	6882	W256	2.0	+4/+62	5/70	1.30/3.27	0.40	+	++
6396	6882	W256	1.0	+14/+59	1/20	1.87/3.61	0.52	±	++
6396	6882	W256	0.5	+23/+62	1/10	2.20/3.84	0.57	±	+
6396	6882	JRS	2.0	+8/+40	8/60	0.42/3.44	0.12	++	+++
6396	6882	JRS	1.0	+8/+39	1/30	0.50/3.39	0.15	++	+++
6396	6882	JRS	0.5	+17/+37	2/20	0.66/3.41	0.19	++	+++
6396	6882	JRS	0.25	+51/+52	1/10	1.53/3.55	0.43	+	+
6396	6882	MRLS	2.0	+12/+35	2/30	3.65/4.10	0.89	−	−
6396	6882	MRLS	1.0	+23/+35	0/10	4.29/4.38	0.98	−	−
20258	3816	R39	1.0	+25/+50	0/10	0.36/1.41	0.26	+	
48225	4383	W256	0.5	+14/+18	1/10	3.33/2.98	1.12	−	++
48225	4383	R39	0.5	+22/+61	2/30	1.18/1.90	0.62	±	++
749	1150	FRC	75	+18/+40	1/10	1.36/1.07	1.27	−	−
755	5357	JRS	20	+16/+17	1/10	2.11/4.37	0.48	+	−
755	5357	MRLS	20	+24/+49	1/10	3.12/4.70	0.66	±	−
3057	1054	R39	100	+21/+23	0/10	2.34/4.10	0.57	±	±
742	9505	W256	2.5	+19/+53	2/20	2.94/3.88	0.76	−	±
742	9505	JRS	2.5	−5/+27	1/15	1.48/3.45	0.43	+	−
739	1072	JRS	0.25	−7/+38	2/10	0.17/4.30	0.04	++	+++
739	1072	R39	0.5	−20/+15	2/10	0.21/1.61	0.13	++	
739	1072	R39	0.25	−5/+31	8/50	0.94/2.60	0.36	+	+
739	1072	R39	0.125	−2/+25	0/10	0.88/2.01	0.44	+	
739	1072	MRLS	0.25	+20/+22	2/15	0.0/4.84	0.0	+++	++
739	1072	MRLS	0.15	+7/+42	1/10	3.46/4.91	0.70	±	++
740	1275	FRC	1.5	+2/+14	0/10	1.18/1.39	0.85	−	−
740	1275	W256	0.5	+37/+28	2/10	1.81/2.77	0.65	±	+
740	1275	JRS	1.5	−7/+38	2/10	0.69/4.30	0.16	++	++
740	1275	R39	1.5	+33/+35	1/20	1.43/2.98	0.48	+	+
740	1275	R39	1.0	−6/+21	2/20	1.80/3.22	0.56	±	+
740	1275	R39	0.5	0/+23	0/10	2.12/1.82	1.16	−	
107136	1414	R39	50	−11/+34	2/20	1.11/2.13	0.52	±	−
9169	2859	W256	150	+26/+58	0/10	2.80/2.70	1.04	−	−
9168	6258	JRS	5.0	+6/+28	0/10	1.33/2.44	0.55	±	±
9168	6258	MRLS	5.0	+13/+31	0/10	4.12/4.68	0.88	−	
26980	19256	W256	1.0	+45/+50	0/10	1.02/3.72	0.27	+	++
26980	19256	JRS	1.0	−14/+44	0/10	0.99/4.57	0.22	++	+++
13875	1905	R39	150	+23/+23	0/10	1.49/4.10	0.36	+	
13875	1905	R39	100	+17/+19	0/20	3.53/3.66	0.96	−	−
36390	436	R39	1.0	−11/+7	0/10	2.04/1.93	1.06	−	−
109229	30000	FRC	167 IU	+62/+51	0/5	1.77/2.44	0.73	±	−
109229	30000	W256	167 IU	+68/+41	0/10	3.19/3.43	0.93	−	−
109229	30000	MRLS	167 IU	+40/+35	0/5	3.72/3.21	1.16	−	−
109229	30000	RFS No. 1	167 IU	+45/+53	0/5	2.83/4.62	0.61	±	±
109229	30000	RFS No. 1	1667 IU	+138/+161	0/5	6.40/5.95	1.08	−	−
109229	30000	RFS No. 1	5000 IU	+50/+83	0/5	3.96/5.16	0.77	−	±
509565	9565	MRLS	2.5	−11/+6	0/10	3.20/4.37	0.73	±	

TABLE 20.—Summary of tumor sensitivity: compounds producing complete tumor inhibition at the MTD or less*

Tumor	Alkylating agents		Pyrimidines, purines, folic acids, and other antimetabolites	Steroids	Antibiotics		Quinolines	Miscellaneous compounds	
	SK No.	NSC No.			SK No.	NSC No.		SK No.	NSC No.
FRC	(23/43)		(0/60)	(0/14)	(6/49)		(0/6)	(1/87)	
	598	10107			20779	—		25513	53582
	15673	8806			28008	—			
	20597	—			28009	—			
	25691	525691			28010	—			
	26407	526407			28146	—			
	25823	525823			28242	—			
	25022	525022							
	26406	526406							
	27453	527453							
	27456	62403							
	24464	23909							
	27702	409962							
	27408	527408							
	11088	41269							
	7505	3052							
	20501	26271							
	20644	520644							
	20646	520646							
	17360	42158							
	1133	9706							
	6882	6396							
	28988	528988							
	4383	48225							
W 256	(2/56)		(0/66)	(0/14)	(1/58)		(0/2)	(0/117)	
	1133	9706			28009	—			
	6882	6396							
JRS	(30/47)		(1/53)	(0/12)	(7/52)		(0/10)	(6/98)	
	598	10107	1072		19256	26980		26071	66248
	1424	9506			28008	—		25513	53582
	15673	8806			28009	—		25512	49403
	21739	14210			28010	—		28239	—
	20598	—			28146	—		21569	37538
	20597	—			28242	—		24784	524784
	25691	525691			25021	56410			
	26407	526407							
	25823	525823							
	26622	526622							
	25022	525022							
	27453	527453							
	27456	62403							
	27702	409962							
	27408	527408							
	11088	41269							
	13595	74437							
	7505	3052							
	4614	49421							
	3818	9717							
	20501	26271							
	20644	520644							
	20645	520645							
	20646	520646							
	20647	520647							

TABLE 20.—Summary of tumor sensitivity: compounds producing complete tumor inhibition at the MTD or less*—Continued

Tumor	Alkylating agents		Pyrimidines, purines, folic acids, and other antimetabolites	Steroids	Antibiotics		Quinolines	Miscellaneous compounds	
	SK No.	NSC No.			SK No.	NSC No.		SK No.	NSC No.
	17360	42158							
	1133	9706							
	6882	6396							
	15385	—							
	28988	528988							
JRS–M–resistant	(0/16)		(0/8)	(0/4)	(0/9)		(0/1)	(0/16)	
R39	(5/8)		(0/12)	(0/3)	(0/6)			(0/15)	
	101	762							
	4614	49421							
	3818	9717							
	1133	9706							
	4383	48225							
YRS	(15/17)		(0/7)	(0/2)	(4/8)		(0/3)	(0/3)	
	101	762			19256	26980			
	25691	525691			28010	—			
	15673	8806			28146	—			
	26407	526407			28242	—			
	25823	525823							
	25022	525022							
	26406	526406							
	27453	527453							
	27456	62403							
	27702	409962							
	29213	529213							
	29102	84641							
	26501	26271							
	1133	9706							
	28988	528988							
MRS No. 1	(1/12)		(0/8)	(0/3)	(1/12)			(0/16)	
	25691	525691			19256	26980			
MRLS	(1/42)		(1/54)	(0/13)	(0/46)		(0/13)	(0/81)	
	20501	26271	29509						
RFS No. 1	(1/5)		(0/10)	(0/2)	(0/3)		(0/3)	(0/10)	
	27702	409962							
RFS No. 4	(0/4)		(0/6)	(0/2)	(0/1)				
RFS No. 6	(3/4)		(1/7)	(0/2)	(0/2)			(0/4)	
	27702	409962	1275						
	20501	26271							
	1133	9706							
RFS No. 7	(2/4)		(0/8)	(0/2)	(0/2)			(0/4)	
	27702	409962							
	20501	26271							
BRK	(0/17)		(0/10)	(0/4)	(0/19)			(0/26)	

TABLE 20.—Summary of tumor sensitivity: compounds producing complete tumor inhibition at the MTD or less*—Continued

Tumor	Alkylating agents		Pyrimidines, purines, folic acids, and other antimetabolites	Steroids	Antibiotics		Quinolines	Miscellaneous compounds	
	SK No.	NSC No.			SK No.	NSC No.		SK No.	NSC No.
NRH	(0/12)		(0/6)	(0/2)	(0/11)			(0/11)	
FOT	(2/21)		(0/11)	(0/7)	(1/24)			(1/20)	
	27702	409962			19256	26980		25512	49403
	20501	26271							
OT	(1/16)		(0/6)	(0/5)	(0/14)			(0/19)	
	20501	26271							
AT	(1/18)		(0/4)	(0/2)	(0/20)			(1/14)	
	27702	409962						24759	35843

*( ) = No. active/total number tested.

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Screening, the Cornerstone of Chemotherapy[1]

Presented at the Screening Contractors Meeting, Hazleton Laboratories, April 14, 1972

Frank M. Schabel, Jr.[2]

Fellow screeners, I salute you! I believe that what we are doing is one of the most important, promising, and potentially rewarding scientific activities we could possibly be engaged in, and I would like to discuss this personal conviction with you.

We are involved in cancer chemotherapy—the discovery and development of chemical agents useful in the treatment of cancer. As such, we are involved in attempting to control a life-threatening disease which will kill about 345,000 Americans in 1972. In addition, it is estimated that there will be approximately 650,000 new cancer cases diagnosed in the United States in 1972. As we all know, prevention is better than cure and all of us support the extensive effort going into studies on oncogenesis. Once the cause or causes of cancer are clearly defined and understood, we will be in a position to prevent the development of new cases. However, the specific etiology, based on objective scientific evidence, of the first human malignant neoplasm has yet to be described. Until effective preventive measures are discovered, developed, and made available, this frightening number of new cancer cases and resulting high mortality continues each year with unrelenting predictability. In all likelihood, these morbidity and mortality statistics will increase significantly in the next 25 years in the absence of prevention and/or improved treatment. This is because approximately 50% of the population of the United States is 25 years of age or under, and about 75% of cancer in humans in the United States appears in individuals 55 years of age or older. As the population age distribution normalizes, as it certainly will in the predictable near future, the absolute number of cancer cases and deaths is bound to increase markedly.

So, we chemotherapists are fighting a large problem which is certain to increase in size if we are limited to current methods of control. We need better cancer drugs, and we screeners are critical to their discovery and development. Many academic scientists are intellectual snobs—they look with disdain on such as we, who, in their opinion, would stoop so low as to conduct such pedestrian work as to screen for medically useful drugs. I reject this prejudiced and stupid attitude out of hand. Many academicians would maintain that we should determine the specific functional differences between normal cells and cancer cells and then synthesize drugs to interfere with the unique functions present in cancer cells but missing in normal cells. This philosophy is intellectually attractive to all of us. The problem is that, with the possible exception of the requirement for asparagine by some tumor cells in the absence of a similar requirement by normal cells, metabolic differences between tumor cells and normal cells of sufficient magnitude to suggest the likelihood of developing curative chemotherapy based on these differences are not known. Still, in this abysmal ignorance, a sufficiently large number of drugs with selective lethal toxicity for tumor cells over normal cells have been discovered by screening methods to convince all of us that additional useful drugs will be discovered by further screening. It is the only available method based on an historical record of past success that we can follow with reasonable assurances that it will lead to the discovery of additional useful drugs. Professor Larin in 1967, in discussing the problems of searching for antiviral drugs, correctly observed and stated that "The discovery and subsequent development of the first synthetic centrally active drugs, diuretics, sulfanamides, cardiac glucosides, and antibiotics, such as penicillin, were in no way influenced by any fundamental knowledge of the processes with which they interfere." Few could seriously question the validity of Larin's statement. In fact, em-

[1] Received Oct 12, 1972; accepted Oct 12, 1972.

[2] Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Ala.

pirical search has been the keystone of both initial discovery and following improvement of nearly all useful chemotherapeutic agents. Hence, my title—"Screening, the Cornerstone of Chemotherapy."

To screen is to examine methodically, in order to make a separation into different groups, and a cornerstone is the most basic element or foundation. It is that from which the main structure rises and upon which it rests, its foundation. Screening has been the most important and most productive method whereby new classes of useful chemotherapeutic agents have been discovered. The great German physician, immunologist, chemist, and chemotherapist, Paul Ehrlich, was the first organized screener for new chemotherapeutic agents. He recognized that different cells in the living state took up dyes differently. From these observations, he developed the so-called magic-bullet concept which presumed that drugs could be found which would kill parasites without unacceptably harming the host.

You're all familiar with the discovery in Ehrlich's lab of the biologic activity of compound 606 (fig 1), the arsenical known as Salversan, which was very active against experimental syphilis in animals, and was subsequently active in man. Ehrlich said that a number of things were necessary to find useful drugs: first, *gerate*—tools or apparatus, and in our hands I believe these tools are useful tumor systems; second *geduld*—patience, endurance, persistence; third, *geschicktlichkeit*—skill and ingenuity; fourth *gluck*—good luck; and, as others have sometimes added to Ehrlich's list, *geld*—money. Our major tool is the tumor-bearing animal. We know that some of our experimental tumor systems are sensitive to many drugs that are also active in naturally occurring neoplastic disease in man.

The best example probably is leukemia L1210 which has demonstrated a high degree of drug response correlation with acute lymphatic leukemia in children. We clearly lack highly reliable predictive experimental tumor systems

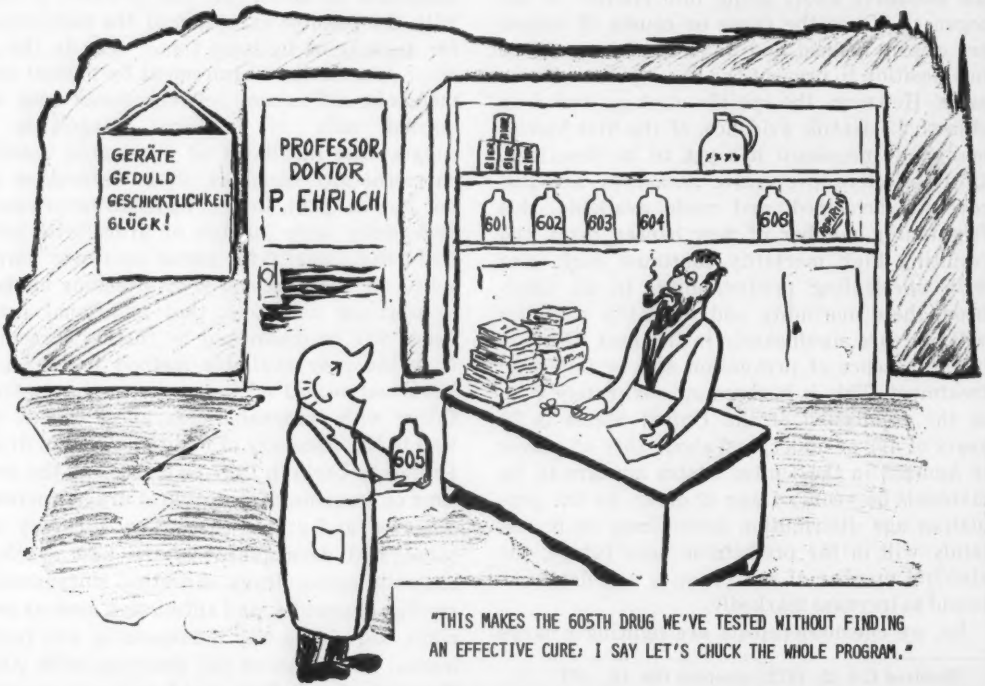

FIGURE 1

for most of the solid tumors in man, and this is an area of extensive ongoing work by Drug Research and Development, Division of Cancer Treatment, National Cancer Institute.

Just to give you a little insight into the ultimate result of a screening activity, let me cite the antibiotic production in the United States. Some potential screener didn't decide that there must be antibiotics in nature which would cure infectious disease and then set out to find them (fig 2). The lead that clearly forced the issue was the observation by Fleming that a strain of Penicillium that had contaminated one of his bacterial culture plates was producing a material that inhibited the growth of Staphylococcus on this plate.

"--chance only favours the prepared mind--"
Louis Pasteur

FIGURE 2

TABLE 1.—Preliminary gross estimates of requirements and phasing of national capacities for expansion of cancer program*

	Current capacity	1973	1974	1975	1976	1977
1. Chemotherapy screening	Approximately 15,000 agents per year processed through 2 fast growing tumor screens and 1 biochemical screen—15 agents survive preliminary screening; toxicology studies performed on 10 agents; clinical workup and pharmacology on 6 agents; ratio of random/selected agents entering screen is 5/1	Increasing screening capacity to 30,000/year →	45,000/yr →	50,000/yr →	level off at	50,000/yr
		Add following types of tumor screens: 2 fast growing, 2 slow growing, 2 biochemical, 2 spontaneous, 2 biologic →	modify screening system as necessary →			
		Ratio of random to selected agents remains same. Mix of agents entering screen will shift to more plant, animal, and marine life products and fewer fermentation products →				
2. Clinical assessment of new drugs and combinations of drugs in specific types of disease	6 new single drugs and 4 combinations of drugs are processed through all phases of drug development leading to clinical assessment	Capacity increased to: 6 new drugs/yr →	6 →	6 →	8 →	10–25/yr
		and 6 more combinations/yr →	8 →	10 →	12 →	15/yr

*From the National Cancer Plan Executive Report, Volume 1, figure IV–4.

Fleming isolated this culture and demonstrated that the inhibitory product from it also inhibited Streptococcus, Pneumococcus, Gonococcus, and the diphtheria bacillus, but did not inhibit coli or the influenza bacillus. Fleming was astute enough to suspect that this inhibitory activity by a common contaminant of his bacterial cultures might in fact have therapeutic potential. The isolation of practically useful penicillin suggested that other similar useful materials might be produced in nature, and this set off a very active screening search for additional antibiotics.

The production of antibiotics in the United States from 1953 to 1969 is shown in table 2. There has been a continuous increase in production during this period up to the present time; currently nearly 4000 tons are being produced each year in the United States. I said earlier that most of the therapeutically useful materials have been discovered and developed without any fundamental knowledge of the process with which they interfere (to a greater or lesser degree by the application of screening methods), and this has resulted in the development of a very large ethical drug industry in the United States.

Table 3 lists the ethical drug sales in the United States in millions of dollars between 1964 and 1970, and I believe that the vast majority of useful ethical drugs had their origins in observations by prepared minds on biologic response of living systems to randomly selected drugs. Screening has been and continues to be the most useful and productive method of detecting potentially useful biologic activity by new classes of drugs. In the past, once the activity of a new drug has been firmly established, then improvement of this activity by congener synthesis of the screening lead has been enormously rewarding; I am sure this will continue to be so in the future. Often, improved biologic activity associated with congener synthesis has not been dependent on any clear understanding of biologic mechanism of action, so this is, in effect, extended screening.

TABLE 2.—Antibiotic production in the US

Year	Tone	Year	Tons
1953	840	1963	2100
1954	900	1964	2000
1955	1200	1965	2350
1958	1300	1966	2700
1959	1150	1967	2600
1960	1500	1968	3000
1961	1650	1969	3650

The highest requirement of a good screener and the most marked difference between him and lesser investigators is his intellectual discipline. If only one in 1000 materials put through a screen shows sufficient activity to warrant further work, it is obvious that if you treat any material going through the screen in a sloppy manner, you only have one chance in a thousand of doing any serious damage. Therefore, one could rationalize that he could treat any single screening candidate lightly without much risk of hazard to the program. The alternative to this escape from intellectual discipline is to live with the constant conviction that any material one screens may be the chemotherapeutic panacea that we all seek, or if not that, at least a potentially useful new anticancer drug. Screening, in my judgment, demands far more intellectual discipline than any other scientific activity, and those of us who do it well are a unique and rare group of laboratory investigators. Charles Kettering once said that 99% of research is failure. With the yield that we can expect from our screening activity, 99.9% is failure, but still each screening test we do must be treated as if it were, in fact, testing the useful new compound that we seek. This intellectual discipline is something that must be within us. No one can really test us; no one can really check on us; no one can really criticize us in our screening activity, if we follow the screening protocol in a "cookbook" fashion.

I believe that we have a great advantage over many others in cancer research, in that if we retain our intellectual discipline in delivering our dedicated competence to this difficult job of screening for new anticancer agents, we will raise the level of new compounds to or above the estimates contained in this plan; and based on the usefulness of anticancer agents similarly discovered in the recent past, we will make very significant contributions to rapidly improving drug therapy of cancer in the predictable near future. I salute you in your technical competence, your intellectual discipline, your

dedication to a very important scientific activity, and I share with you the certain knowledge that working with our sponsors in the national cancer effort, we will contribute significantly to the development of new and better drugs for cancer therapy.

TABLE 3.—Ethical drug sales in the US (× $1,000,000)

	1964	1966	1968	1970
Antibiotics	356	450	570	556
Tranquilizers	210	280	350	430
Cardiovasculars	135	185	215	257
Hormones	215	274	331	395
Vitamins and nutrients	200	220	235	248
Analgesics, antacids, antiarthritics, antihistamines, antiobesity, antispasmodics, cough and cold, diabetic therapy, diuretics, hematinics, muscle relaxants, psychostimulants, sedatives, sulfonamides	783	951	1102	1404
Others, including biologicals	667	802	827	910
Total ethical sales	2566	3162	3630	4200

Consideration of the Subcutaneously Implanted B16 Melanoma as a Screening Model for Potential Anticancer Agents [1,2]

Presented at the Screening Contractors Meeting, Hazleton Laboratories, April 14, 1972

D. P. Griswold, Jr.[3]

In the selection of an animal tumor system as a screening model for potential anticancer agents, two pertinent questions must be asked:

1. Is the model predictive for some part of the human problem?
2. Can the model be manipulated with relative ease to provide reliable, reproducible, quantitative data?

The first question can be answered only in retrospect—after a correlation can be made between results from the model and from man. But if the question is rephrased to ask:

Is the model likely to be predictive?

then perhaps judgment as to its usefulness can be made prior to its actual use as a screening tool, thus providing a means for narrowing the list of models for trial as screening tools.

What the screen is intended to detect, of course, is agents with specificity. So, in the selection of the model, one must bear in mind those factors that most likely contribute to specificity of action. Among those factors are:

1. Biochemical (eg, differences between normal and neoplastic tissues, ie, site of action, blocks, etc),
2. Pharmacologic (such as drug activation, inactivation, distribution), and
3. Growth characteristics (which include growth fraction, G_0 populations, lag time, etc).

Such outlines are helpful in organizing one's thoughts but are often misleading in that the implication is made that these are distinct, limited, and separate criteria when, in fact, there may be considerable interrelationship and possibly other factors.

The requirement of some leukemic cell populations for the nonessential amino acid, asparagine, where the mouse lymphosarcoma P1798 is a model, is probably the best evidence in favor of specific biochemical differences between normal and tumor tissue (1–4). The activation of cyclophosphamide [4] by mammalian liver can be explained on a pharmacologic basis (5,6), but observed differences in sensitivity between low growth-fraction tumors and normal tissues to cycle-specific agents have not yet been adequately explained. Nor is the antitumor activity of the cycle-specific agent 5-fluorouracil [5] understood when the agent is given as a single dose, although the basis for activity is possibly pharmacologic, having to do with the rate of activation to 5-fluorodeoxyuridylic acid (7). And, of course, other factors, such as the inherent sensitivity of hormone-dependent cells, must be considered. But without question, the greatest single factor for explanation of the successes realized to date in the chemotherapy of tumors of animals and man can be described by the third factor, growth characteristics. It has been recently pointed out that the greatest chemotherapeutic successes have been achieved with ten of at least 100 different types of cancer, that those ten share the common characteristic of rapid growth, and that recognition of the interdependence of growth pattern and drug susceptibility has made possible the rational selection of animal models for detection of active drugs (8).

The question *now* is: how well does B16 melanoma fit this rationale? That is, is it likely to be predictive for some part of the human problem and will its use provide reliable quantitative data? I think those questions may best be

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[2] Supported by contract NIH-71-2098 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

[3] Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Ala.

[4] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetahydro-, 2-oxide, monohydrate; Cytoxan.

[5] 5-Fluorouracil; NSC-19893; CAS reg. No. 51-21-8.

answered by comparison of B16 melanoma with other tumor systems.

L1210 ascites (L1210 leukemia in BDF_1 mice [C57BL female × DBA_2 male]) is similar to some human leukemias both from morphologic and behavioral standpoints (9). Its value as a screening tool and predictor for those leukemias has been proved. The hamster plasmacytoma (Fortner plasmacytoma No. 1 in the Syrian golden hamster) and spontaneous AKR lymphoma (spontaneous AKR lymphoma in AKR mice) appear to be morphologic and behavioral counterparts as well as adequate predictors for some human lymphomas and myelomas (10–14). None of these experimental tumors, however, adequately represent the spectrum of *solid* tumors in man where, in fact, the greatest part of the problem lies.

Earlier I mentioned that similarity of growth was a proven common denominator by which a rational selection of models could be made. I also mentioned that among those known factors influencing drug specificity, interrelationships probably exist. I mention this again only to suggest that many of those tumors that have similar growth characteristics seem also to share some similarities in morphology or architecture and as a reminder of the growing feeling (admittedly based mostly on soft data) that tumor architecture may effect the pharmacologic and growth characteristic factors involved in drug specificity. I think this is worth remembering so that in considering the growth and drug-response characteristics, one will not lose sight of other parameters that may affect the usefulness of an experimental tumor as a model.

For comparison, the cell cycle parameters and volume doubling times of representatives of three classes of experimental tumors (where class is based on growth rate) are shown in table 1 (15). Interestingly, the lengths of the S phase of all three tumors (L1210 leukemia, plasmacytoma, and B16 melanoma) are quite similar (9.0, 8.8, and 7.0 hours), although the B16 melanoma has a much longer median T_c—20 hours compared to 12.8 and 13.8. Furthermore, the labeling index of the proliferative fraction of B16 melanoma is markedly lower (29%) than those of L1210 or plasmacytoma, and the calculated proliferative fraction of only L1210 approaches 100%. The volume doubling time of L1210 is rapid and almost exponential throughout most of its growth history. While the growth curve of plasmacytoma is distinctly asymptotic, the doubling time does not exceed about 6 days at 10 g. The volume doubling time of B16 melanoma on the other hand may range from about 1 day at 0.1 g to near infinity at 10 g.

TABLE 1.—Cell cycle parameters (data of L. Simpson-Herren)

Tumor	Days after implant	Mean harvested weight (mg)	T_s (hrs)	T_c (hrs)	T_s/T_c	Thymidine index	Labeling index	Proliferation fraction
L1210 leukemia	0	(10^5 cells)	9.0	12.8 (0.53 days)	0.70	(0.60)	0.70	0.86
Plasmacytoma No. 1	6	493	8.8	13.8 (0.58 days)	0.64	0.14	0.62	0.23
B16 melanoma	9	560	7.0	20 (0.8 days)	0.35	0.16	0.29	0.55

Rate of volume doubling (days)

Tumor	Median day of Death	Tumor weight (g)				
		0.1	0.5	1.0	5.0	10
L1210 leukemia	8.2 (10^5 cells)	(0.4–0.6 from 10^3–10^5 cells)				
Plasmacytoma No. 1	20	0.9	1.5	1.9	3.5	6.0
B16 melanoma	24	1.2	1.5	2.1	7.0 > 45	

In fact, of 11 commonly used experimental tumors, we have found only three that have markedly longer volume doubling times than B16 melanoma; eg, at 0.1 g, the Lewis lung tumor has a doubling time of about 2.0 days, first generation C3H breast tumor about 3.2 days, and the DMBA-induced breast tumor about 4.6 days.[6]

These growth rate differences are probably best summed up in figure 1 where L1210 ascites (curve A) appears in the most rapidly growing class; plasmacytoma (curve J) appears in the middle, slower growing and less responsive class; and B16 melanoma (curve M) falls in the third class of slowest growing tumors which also seem to be least sensitive to chemotherapy.

Another grouping, based on morphologic classification, also separates these three representative tumors. L1210 ascites is in a dispersed cell form which allows maximum exposure of trial agents to the cell population. The subcutaneously (sc) implanted plasmacytoma, sometimes called an aleukemic leukemia, grows in a solid form but without the well-organized appearance around blood vessels as seen in many truly "solid" tumors, such as B16 melanoma.

Knowledge of architectural characteristics of experimental tumors would seem to be of some importance in the selection of "model systems" because of the work of Tannock (16), and, more recently, Jirtle and Clifton (17), who have suggested the existence of relationships of growth and chemotherapeutic responsiveness to tumor vasculature.

A short time ago my associates and I worked extensively with a hamster melanoma (18,19) which had characteristics of morphology and slow growth similar to B16 melanoma. It was not, however, as useful to us as we had hoped—not only because of the delicate nature of its host but primarily because of our inability to adequately disassociate the tumor cells after treatment for assay and because of the erratic tumor mass behavior after treatment. *The ability to quantitate with some precision is just as important to a model as any characteristics it may share with its counterpart.*

Two accepted methods of measuring chemotherapeutic effectiveness are (*a*) in vivo or in vitro assay for clonogenic cells, and (*b*) delay in tumor appearance to a given size. Host lifespan is also useful in some situations, but generally reflects drug effects on metastatic disease and may or may not correlate with effects on the primary tumor.

In order to make "delayed-tumor-appearance" data meaningful in terms of percent tumor cell kill, we have in the past—rather

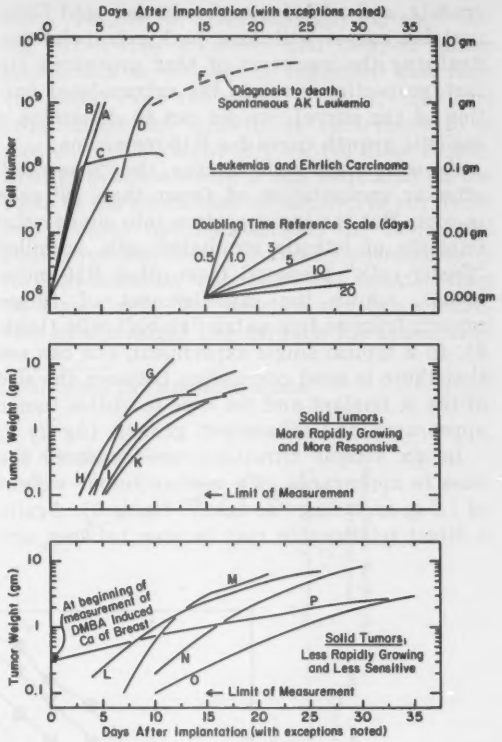


FIGURE 1.—Growth rate comparisons of various experimental animal tumors (data of H. E. Skipper). *A*. L1210 leukemia (ip), mouse. *B*. L1210 leukemia or long-passage AK leukemia (iv), mouse. *C*. Ehrlich ascites carcinoma (ip), mouse. *D*. Solid L1210 leukemia (sc), mouse. *E*. First-passage AK leukemia (iv), mouse. *F*. Advanced spontaneous AK leukemia (estimated), mouse. *G*. Walker carcinoma 256 (sc), rat. *H*. Sarcoma 180 (sc), mouse. *I*. Carcinoma 755 (sc), mouse. *J*. Plasmacytoma (sc), hamster. *K*. Solid Ehrlich carcinoma (sc), mouse. *L*. Lewis lung carcinoma (sc), mouse. *M*. B16 melanoma (sc), mouse. *N*. Melanotic melanoma (sc), hamster. *O*. First-passage mammary tumors (sc), mouse. *P*. DMBA-induced carcinoma of breast, rat.

[6] Simpson-Herren L. Unpublished data.

crudely, and with tongue-in-cheek—used Gompertzian curves with long back extrapolations. Realizing the weakness of that procedure (in fact, suspecting error in the extrapolated portion of the curve), we set out to determine a realistic growth curve for B16 melanoma.

As with many solid tumors, the "take-rate" after sc implantation of fewer than 10^6 cells is poor. But the incorporation into similar-size implants of lethally irradiated cells, so-called "feeder cells" prepared from other B16 melanomas, allows the establishment of tumor growth from as few as ten "viable" cells (table 2). In a typical single experiment, one can see that there is good correlation between the size of the sc implant and the time to visible tumor appearance and subsequent growth (fig 2).

In six similar titrations, we measured the time to appearance at a median tumor weight of 1.0 g, excluding "no-takes" (table 3). Again, a direct relationship may be seen between size of implant and time to appearance; and the ranges from experiment to experiment for each similar-size titration are quite small. Using those "time-to-appearance" data along with

TABLE 2.—Tumor incidence after sc implantation of B16 melanoma in BDF_1 mice. Mechanically dispersed, hemocytometer-counted cells were suspended for dilution in Locke's solution or in a 20% w/v brei of lethally irradiated (10,000 R ^{60}Co) B16 melanoma cells.

Size of implant (No. viable cells)	Without "feeder cells"	With "feeder cells"
10^7	100%	100%
10^6	51%	100%
10^5	4%	96%
10^4	2%	94%
10^3	4%	74%
10^2	0%	71%
10^1	0%	27%
None	5×10^7 "feeder cells" only	0%

Pooled data from 3 experiments

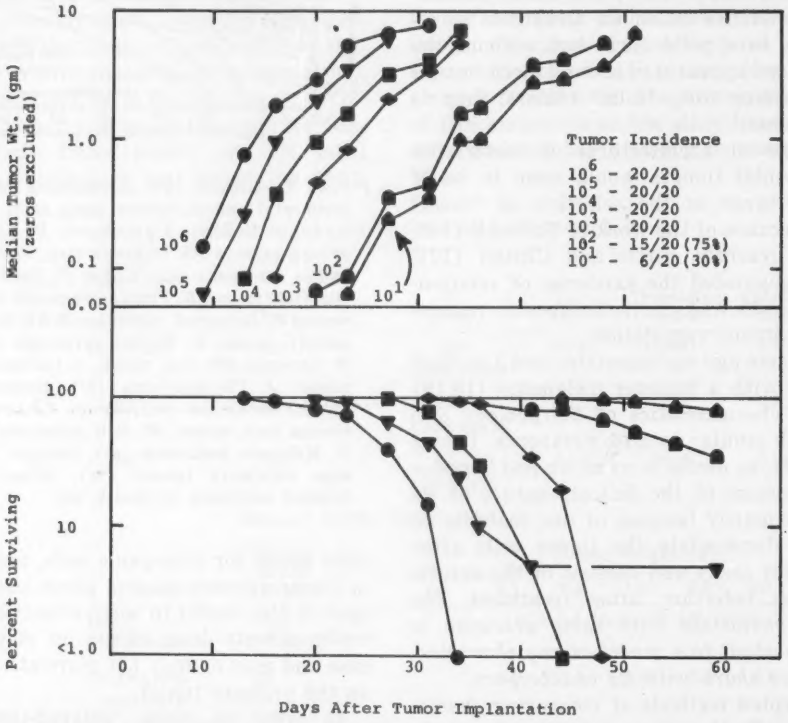


FIGURE 2.—Relationship of size of sc implant (No. of cells) of B16 melanoma with "feeder cells" to time of median tumor appearance and host lifespan.

measured tumor weights from all of the titrations from the six experiments, we attempted to prepare a composite growth curve down to ten cells, using a computerized Gompertzian equation (20) (fig 3). The incorporation of all data points resulted in a poor fit. That is, the curve did not fairly represent the data points.

Elimination of those points at 10^1- and 10^2-cell implant sizes gave a curve that was a good fit to the remaining data but widely missed the two excluded points. The extrapolation of this curve, curve "A," projected a time requirement of about 26 days for one cell to reach 10^0 cells or a weight of about 1.0 g. It also indicated a mass doubling time of 0.4 day at 1.0 cell. Previous results of chemotherapy trials,[7] using tumor-free survivors and delayed tumor appearance as end points, suggested that time (26 days) was too short. That is, the time requirement for growth or recurrence to a median tumor weight of 1.0 g (in those chemotherapy trials wherein it was estimated on the basis of the percentage of tumor-free survivors and Poisson distribution that the tumor cell population had been reduced by chemotherapy to approximately one cell) was greater than 26 days. Curve "B," which is simply an extension of a straight line through the appearance

[7] Griswold DP. Unpublished data

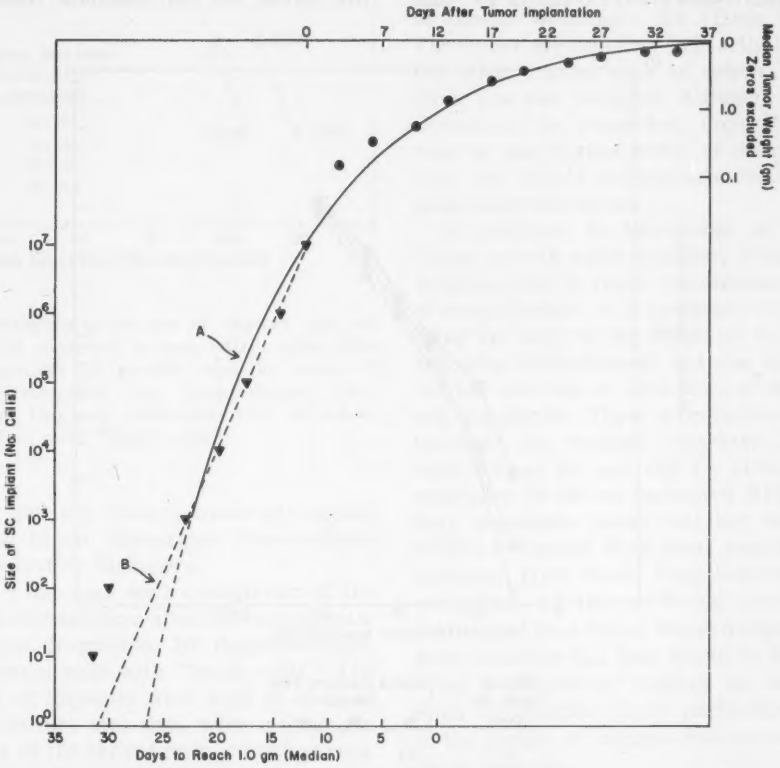
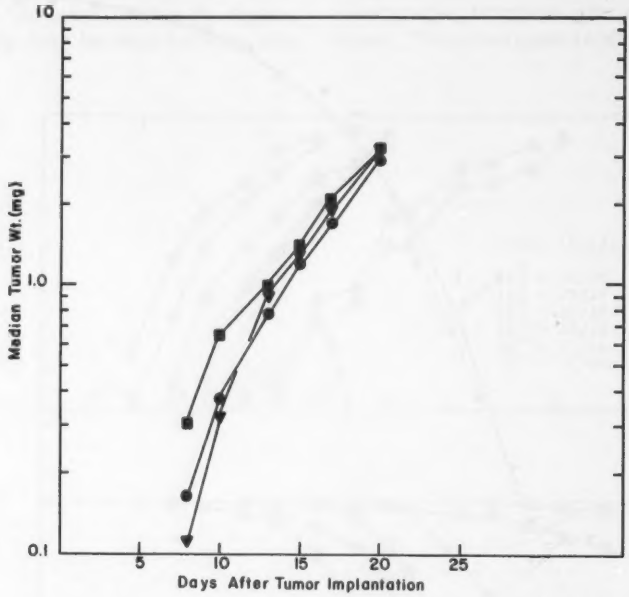


FIGURE 3.—Gompertzian-fitted growth curve of sc implanted B16 melanoma with "feeder cells." Data were taken from experiments indicated in table 3. Tumor weights from the 39 cell titrations were pooled for determination of medians by adjustment of the time based on actual time to "appearance" (*see* table 3) of tumors from each titration. ● = median tumor weights from caliper measurements. ▼ = days to appearance at 1.0-g median tumor weight. A = Gompertz-fitted curve with extrapolation below 10^3 cells. B = Visual line, 10^7-10^3 cells with extrapolation below 10^3 cells.

TABLE 3.—Comparison of appearance times of sc implanted $\log_{10}$ dilutions of B16 melanoma cells with "feeder cells"

	Time (days) from sc implantation to 1.0 g (median tumor weight)						
No. cells implanted:	10^7	10^6	10^5	10^4	10^3	10^2	10^1
Experiment No.							
976-S	12	15	19	20	23	30	31
976-U	12	16	19	20	20	27	32
1048-B_1	13	14	17	22	24		
1053-B_2	12	15	16	18	20	24	27
1053-C_2	12	14	17	19	24	31	36
1053-D_2	11	14	18	21	23	31	
Median:	12	14.5	17.5	20	23	30	31.5
Tumor incidence:	98%	100%	94%	93%	75%	77%	39%

times from 10^7 to 10^3 implant sizes, appears more realistic in that the time requirement for growth or recurrence from 1.0 cell to 10^9 cells more closely approximates the time requirement for recurrence after chemotherapy. Thus, using this curve, we can estimate reasonably well



Median Tumor Wt. (gm)	Volume Doubling Time (days)		
	●	■	▼
0.1	1.63	2.13	1.31
0.5	2.83	3.17	2.28
1.0	4.16	4.03	3.37

FIGURE 4.—Comparison of growth of B16 melanoma in BDF_1 mice after sc implantation of: ● trocar fragments, ■ 10^7 dispersed cells with "feeder cells," or ▼ 10^7 dispersed cells without "feeder cells." Data described by a Gompertz equation to provide the volume doubling time indicated. Pooled data from 3 experiments.

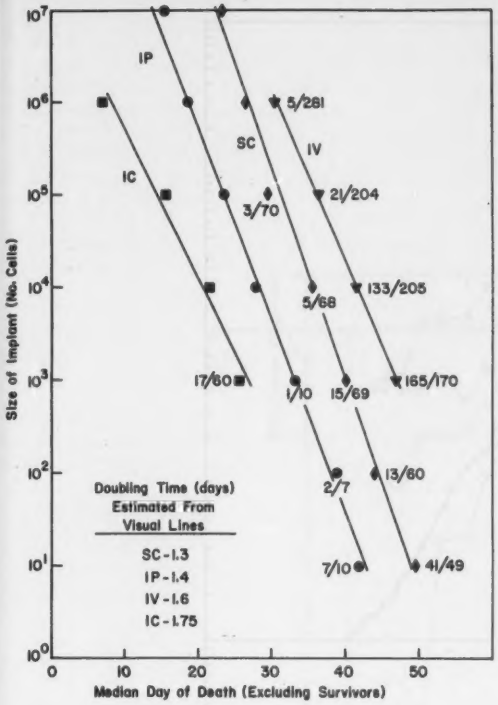


FIGURE 5.—Relationship of size of implant (No. of cells) of B16 melanoma to host (BDF, mice) lifespan; comparison of growth rates by route of implant: intracerebral (ic), intraperitoneal (ip), subcutaneous (sc), and intravenous (iv). Ip and ic implants given with "feeder cells."

the percent cell kill from a treatment—using only delayed tumor appearance time without having to resort to bioassays.

In figure 4 one may see a comparison of the growth of B16 melanoma after the sc implantation of trocar fragments, 10^7 dispersed cells, or 10^7 dispersed cells with "feeder cells." The three types of implants were used in each of three experiments and data were pooled for construction of the three tumor growth curves. Description of the growth curves by a computerized Gompertzian equation allowed the determination of volume doubling times at specified tumor sizes of each of the three curves for further comparison. There appeared to be little difference in growth rates regardless of the type of implant used.

The tumor may be implanted by a variety of routes: intravenous (iv), intracerebral (ic), and intraperitoneal (ip), as well as sc. The relationship between size of implant and host lifespan is good in each instance (fig 5). This affords an opportunity to investigate chemotherapeutic activity against this tumor in a variety of sites and in different growth situations.

B16 melanoma does not metastasize from sc implants with the predictability of the Lewis lung tumor (22). We have been unable to detect metastasis in some few mice either by bioassay, by autopsy at the time the animals were killed, or by complete surgical removal of the primary tumor as late as the median day of death (fig 6) of the total group; however, all mice bearing sc tumors eventually die (from metastasis). The tumor metastasizes primarily to the lungs, but other organs, such as spleen, kidney, and liver, are also involved. Although the rate of metastasis is somewhat unpredictable, this trait is also characteristic of many tumors of man, and should not preclude its use as a surgical adjuvant model.

In addition to knowledge of metastasis, tumor growth rates, and host lifespan characteristics, and in order to interpret the effects of chemotherapy, it is necessary to know something not only of the extent of tumor cell kill following chemotherapy but also of the rate of cell kill and rate of recurrence of the surviving cell population. These parameters can be determined by multiple bioassays after treatment. It can be seen (fig 7), after single-dose treatment of the sc implanted B16 melanoma, that maximum tumor cell kill was obtained within a shorter time than would have been predicted from tumor mass behavior and that recurrence of the surviving population was more rapid than tumor mass changes suggested. Such behavior has been found to hold true for other experimental tumors as well (10,23). Such information is of particular usefulness in the design of multiple-dose or -course treatment regimens.

In conclusion, we find that the B16 melanoma has a relatively long volume doubling time, a moderately small growth fraction, and some morphologic similarities to other "solid" tumors. The titrating ability of the sc implanted tumor allows assays for surviving

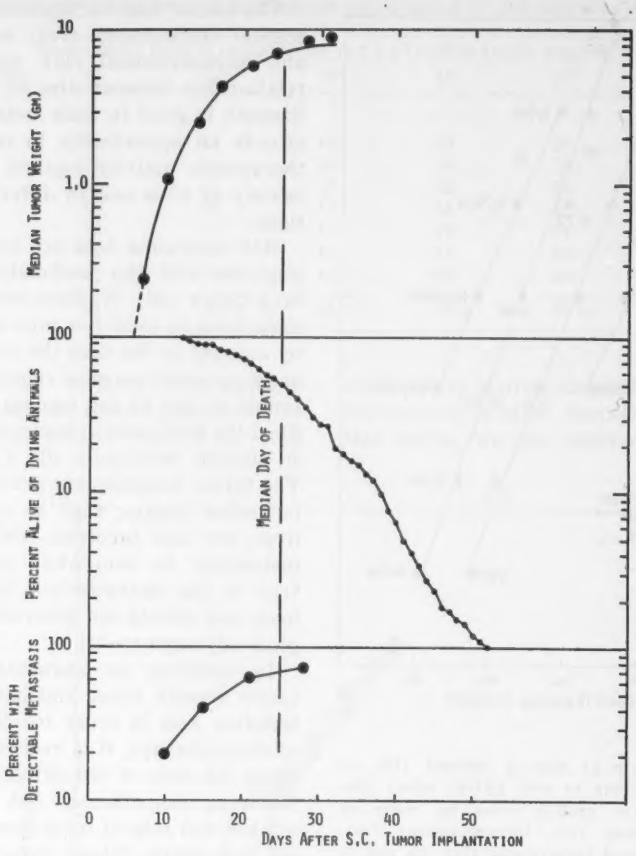


FIGURE 6.—Comparison of Gompertzian-described primary tumor growth, host survival, and percent mice with detectable metastasis after sc implantation of B16 melanoma in BDF_1 mice: metastasis determined by sc bioassay of various tissues (principally lung) or by autopsy at fixed intervals after sc implantation of tumor fragments.

viable cells and chemotherapy trials against small numbers of cells. The establishment and definition of a growth curve allows measurement of percent cell kill without tedious assays. The feasibility of using several implant routes allows testing for chemotherapeutic activity against tumors at various specific sites. Knowledge of the rate and extent of metastasis of the B16 melanoma allows its use as a surgical adjuvant model; and knowledge of the rate of cell kill and recovery provides a basis for design of dosage and schedule-dependency studies where the variables are (*a*) class of agent, (*b*) dosage, (*c*) number of treatments or courses, and (*d*) interval between treatments or courses.

These characteristics, together with the reproducible behavior of this tumor system, suggest that it may be suitable as a model and for trial in the chemotherapy screening program for primary and secondary evaluations.

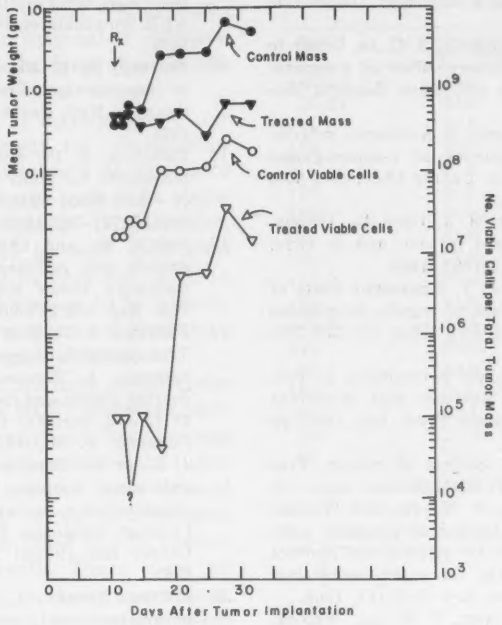


FIGURE 7.—Rate and extent of tumor cell kill and rate of recovery of sc implanted B16 melanoma in BDF_1 mice: determined by intracerebral bioassay after treatment with methyl-CCNU (NSC-95441), 36 mg/kg, ip, Day 11 only.

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Biologic Characterization of the Subcutaneously Implanted Lewis Lung Tumor [1,2,3]

Presented at the Screening Contractors Meeting, Hazleton Laboratories, April 14, 1972

Joseph G. Mayo [4]

The Lewis lung carcinoma was discovered by Dr. Margaret R. Lewis of the Wistar Institute in 1951. This tumor originated spontaneously as a carcinoma of the lung of a C57BL mouse.

The Lewis lung tumor is maintained in our laboratories by subcutaneous (sc) implant of tumor fragments (approximately 25 mg) into C57BL/6 mice with passage every 14 days. Fourteen days after fragment implantation, the tumor averages 2–2.5 g, with individual tumors ranging from 600 to 4000 mg (4 g) in size. The tumor does not appear to be grossly hemorrhagic. In fact, the majority of the tumor tissue is a semifirm homogenous mass.

For experimental work, we have replaced the C57BL/6 mouse with the BDF_1 mouse as indicated in the Drug Research and Development (DR&D) protocol. Table 1 presents data taken from 18 control groups selected from several sc implanted Lewis lung tumor experiments. We obtained 100% tumor takes in 205 control mice in the 18 experiments. There were no spontaneous regressions and no survivors. Median day of death from the 18 experiments was Day 25, with a range of medians of 21.0–32.0 days, and a range of deaths in individual mice of 11–45 days.

The growth of the sc implanted Lewis lung carcinoma is well described by a Gompertz function, and the doubling time increases from 1.7 days for a 0.1 g tumor (100 mg) to 7.7 days when the tumor size reaches 5.0 g (fig 1).

TABLE 1.—Lifespan of BDF_1 mice implanted sc with Lewis lung tumor fragments

Expt No.	Median lifespan (days)	Range of deaths	Survivors/ total
36(1)	29.0	21–34	0/10
36(2)	24.5	21–28	0/10
104-B	27.0	20–35	0/20
109	24.0	22–31	0/10
111	27.5	22–34	0/10
117	24.5	15–34	0/20
128	24.0	22–33	0/10
129	32.0	21–45	0/10
130	28.0	22–32	0/10
137-A	28.0	25–31	0/10
138	21.0	13–29	0/16
142-A	24.5	11–33	0/10
143	28.0	23–34	0/10
90	24.0	16–34	0/10
93	30.0	27–36	0/9
97	21.5	16–32	0/10
98	24.0	19–28	0/10
24	25.5	16–35	0/10
All expts combined	25.0	11–45	0/205

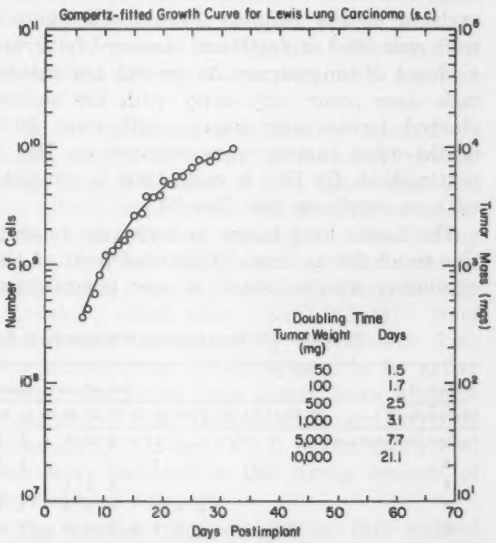

FIGURE 1.—Gompertz-fitted growth curve for Lewis lung carcinoma (sc).

[1] Received Oct 12, 1972; accepted Oct 12, 1972.

[2] Supported by contract NIH-71-2098 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in the text are included in the List of Compounds at the end of the text.

[4] Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Ala.

The mean values for the length of the cell cycle (T_c = 16 hours) and the S phase (T_s = 9 hours) of this cycle do not change significantly when the mean tumor weight increases from 0.3 to 2.7 g, but the thymidine index (TI) decreases from 35% to 18%. This would indicate that there is a decrease in the percentage of cells cycling as the tumor grows larger, but the actual time of the cell cycle (T_c = 16 hours) remains the same.

This decrease in the proliferative fraction observed with the Lewis lung carcinoma as the tumor grows larger would account for the observed increase in time to double over this period (table 2). We can observe that the time to double does increase rather quickly from 2.4 days with a 350-mg tumor on Day 6, to 4.4 days with a 1530-mg tumor on Day 12, to 23 days with a 6400-mg tumor on Day 24, post-sc implant.

After sc implant, this tumor quickly metastasizes to the lungs. In the experiment which is summarized in table 3, animals were anesthetized and sc implanted tumors were removed surgically on Days 2, 4, 6, 8, 10, and 12 post-tumor implant, respectively, in the different groups. Death of the animal (in which the primary tumor was removed) was considered to be due to tumor metastasis, which would have had to occur on or before the time of surgical excision of the primary tumor. All animals were autopsied at death and observed for gross evidence of lung tumor. As we can see, metastasis does occur very early with the sc implanted Lewis lung tumor, with over 50% deaths when tumors were removed on Day 2 postimplant. By Day 6, metastasis is complete with no survivors past Day 33.

The Lewis lung tumor is relatively insensitive to all the antimetabolites and most of the alkylating agents tested in our laboratories.

TABLE 2.—Average growth rate of the solid Lewis lung tumor after sc implant of approximately 25-mg trocar fragments

Days postimplant	Average primary tumor weight (mg)	Average time to double at weights indicated (days)
6	350	2.4
8	620	2.9
12	1530	4.4
16	2920	6.7
20	4615	11
24	6400	23

Cyclophosphamide is effective against the early implanted Lewis lung tumor and against advanced cases of the metastasized Lewis lung tumor when used as a surgical-adjuvant agent. However, cyclophosphamide is relatively ineffective in regressing established (approximately 400-mg) sc Lewis lung tumors.

The Lewis lung tumor is very sensitive to some of the nitrosoureas. A large group of nitrosoureas (approximately 45), all of which were active against L1210 leukemia, have been tested against the established (approximately 400-mg) sc Lewis lung tumor. Tumor growth curves were prepared using caliper measurements made to the median day of death.

A wide range of activity was observed with three clinically useful nitrosoureas, methyl-CCNU, CCNU, and BCNU, given at optimal doses and schedules (fig 2). Methyl-CCNU produced total tumor regression with 30% cures. CCNU produced tumor regression, but no cures, and BCNU produced little or no tumor regression and no cures. Results from the testing of the other nitrosoureas against the sc Lewis lung tumor are not included, but the tumor growth curves would fall somewhere in an area approaching that of methyl-CCNU, which would indicate antitumor activity, up to the control tumor curve, which would indi-

TABLE 3.—Study of tumor metastasis in BDF_1 mice after sc implant of Lewis lung tumors

Day of surgery (postimplant)	Day of death (postimplant)																															120th day: survivors/ total	Median day of death (dying)
	13	14	16	19	22	23	24	25	26	27	28	29	30	31	32	33	35	36	37	39	40	43	44	45	48	68							
Control (without surgery)								1	1	2	5	5	4	1	1																	0/20	29.0
2								1						1	1	1	1		1	1	1	1	1	2	1	1							6/20	39.5
4										1	1	1			2	1	2	1		1	1		1										5/20	35.5
6						2	2	2	1	1	5	3	1	1	1																			0/20	28.0
8				1			2	3	3	1	6	3			1																			0/20	27.5
10	1	1			1	1	2	1	7	2	3	1																						0/20	26.0
12			1			1	2	7	5		1	1		2																				0/20	25.0

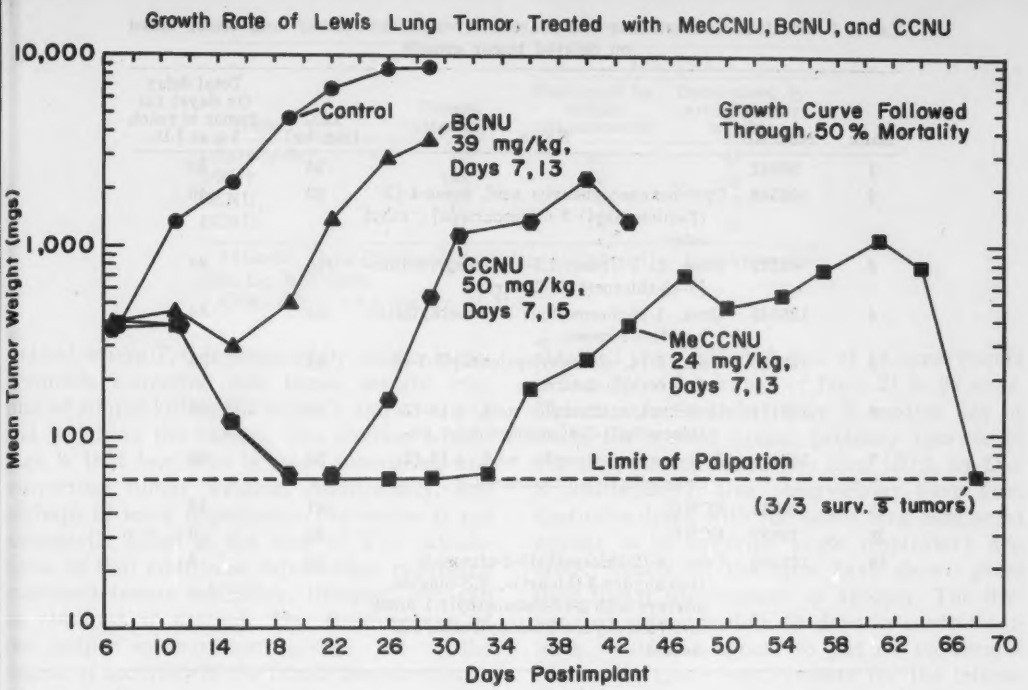

FIGURE 2.—Growth rate of Lewis lung tumor treated with methyl-CCNU, BCNU, and CCNU.

cate little or no activity against the 400-mg tumor.

We have evaluated some of the Lewis lung tumor experimental data in our laboratories using four different methods. Each of these methods could conceivably be adapted to the screening system. The methods that we have considered are:

1. Delay in days in tumor growth (T–C) to a specified size, 500 mg or 1 g, as estimated by caliper measurements converted to weight.
2. Comparison of tumor size of treated animals against tumor size of control animals (T/C) obtained by caliper measurements on Day 12 postimplant, as described in DR&D Protocol 11.
3. T/C obtained by killing the animals and removing the tumor on Day 12 posttumor implant, as described in DR&D Protocol 11.
4. Increase in lifespan expressed as percent.

A total of 28 nitrosoureas were evaluated and ranked according to effectiveness in delaying tumor growth to 500 and 1000 mg. The established 400-mg tumor was used for this evaluation.

Table 4 represents selected nitrosoureas from the 28 compounds, giving the rank and the total delay in days to reach 1 g in tumor size. The two nitrosoureas which we presently consider to be most effective against the Lewis lung tumor (methyl-CCNU and cyclohexanecarboxylic acid, *trans*-4-[3-(2-chloroethyl)-3-nitrosoureido]-, ethyl ester [NSC-103548]) were ranked first and second by this system. Two new nitrosoureas, which appear to be active against the Lewis lung tumor from a single experiment, were ranked sixth and seventh. Although BCNU and CCNU ranked fairly low, they were included in this group because of their clinical interest.

The number that we get by this method (delay in days) would appear to be satisfactory for the screening cards. I am sure that from the

TABLE 4.—Evaluation of various nitrosoureas vs established Lewis lung tumor based on delayed tumor growth

Rank	NSC No.	Name	LD_{10} (mg/kg)	Total delay (in days) for tumor to reach 1 g at LD_{10}
1	95441		36	54
2	103548	Cyclohexanecarboxylic acid, *trans*-4-[3-(2-chloroethyl)-3-nitrosoureido]-, ethyl ester	29	46
3	93372	Urea, 1, 1'-(*trans*-1,4-cyclohexylene)bis-[3-(2-chloroethyl)-3-nitroso-	165	39
4	125649	Urea, 1-(2-fluoroethyl)-3-(4-methylcyclohexyl)-1-nitroso-	44	34
5	132920	Urea, 3-(4,4-dimethylcyclohexyl)-1-(2-fluoroethyl)-1-nitroso-	52	34
6	153174	Cyclohexanecarboxylic acid, 4-[3-(2-chloroethyl)-3-nitrosoureido]-, *cis*-	30	32
7	153175	Cyclohexanecarboxylic acid, 4-[3-(2-chloroethyl)-3-nitrosoureido]-, *trans*-	30	32
20	409962	BCNU	41	12
22	79037	CCNU	38	9
28	121246	Urea, 1-(2-chloroethyl)-1-nitroso-3-(tetrahydro-3-thienyl)-, *S,S*-dioxide, mixture with 3-(2-chloroethyl)-1-nitroso-1-(tetrahydro-3-thienyl)urea, *S,S*-dioxide	16	4

available data, a reliable "cut-off" day could be determined. Although these experiments were initiated with 400-mg tumors, we have sufficient data to feel confident that the T–C (delay in days) system will work with early treatment schedules.

The time and expense involved in making the necessary tumor measurements, conversions, plots, etc, in order to determine the delay to specified tumor size, may well preclude the use of this method in the primary screening program.

The T/C obtained by caliper measurements is dependent upon conversion of these measurements into weight using the following formula:

$$w = \frac{a \times b^2}{2}$$

where a = length in mm, b = width in mm, and w = weight in mg.

The assumption is made that the two short axes are the same length (width and depth) and that the specific gravity is approximately one. This is described in the DR&D Protocol 11.301.

Many comparisons have been made to test the accuracy of T/C obtained by caliper measurements, as described, with that determined by killing mice and weighing the tumors. We ran a small experiment in one of our laboratories in order to test our own accuracy with the Lewis lung tumor (table 5). In this experiment, groups of 20 BDF_1 mice were treated with a single dose of the indicated drug on Day 2, post-sc tumor implant. An additional 20 untreated tumor-bearing mice were held as a control group. On Day 12 postimplant, tumors were measured with vernier calipers in both treated and control groups and the tumor measurements converted into weights as described. After making the measurements, animals were killed and tumors removed and weighed according to standard DR&D protocol.

The excellent correlation observed in table 5 between the estimated T/C and the actual T/C indicates that if measurements are carefully made, we can expect to obtain an acceptable degree of accuracy with caliper measurements converted into tumor weight using the formula described.

There are certain advantages of using the

TABLE 5.—Comparison of two methods of determining T/C (percent)

Name	Dosage (mg/kg)	T/C (%)	
		Estimated by caliper measurements	Determined by actual tumor weights
L-Sarcolysin*	19	41	41
5-FU†	142	56	62
CCNU	57	0	0
BCNU	41	10	10

*Alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, monohydrochloride, L-; NSC-8806.

†NSC-19893; CAS reg. No. 51-21-8.

method where T/C is obtained by caliper measurements converted into tumor weight over that of simply killing the animals and removing and weighing the tumors. One obvious advantage is that less time is spent measuring and converting tumor weights. Additionally, and perhaps of more importance, the mouse is not necessarily killed at the time of T/C calculations, so that additional information regarding sustained tumor inhibition, lifespan, etc, can be obtained if desired. The disadvantage of the caliper measurement system lies in the degree of accuracy of the tumor measurements. Of course, there is a possibility of human variability with different people making these measurements.

The system where T/C is obtained by killing mice and removing and weighing tumors gives an accurate indication of relative tumor inhibition at the time of testing (Day 12 presently). However, by the same token, this is only a "one-shot" deal. Since the mouse is dead and the tumor is gone, no further information is available regarding prolonged tumor inhibition, etc.

The last system that we have considered for early treatment evaluation is the percent ILS (increase in lifespan). The median day of death (dying) of untreated tumor control animals obtained from collected data of 18 experiments is Day 25 with a range of from 21 to 32 days. This is a fairly tight range in median day of death for a solid tumor, probably because of the early metastasis to the lung (50% by Day 2 postimplant). Our observations have been that mice dying with the Lewis lung carcinoma appear to be suffering acute respiratory distress. Nearly all the mice have shown gross lung tumor involvement on autopsy. The lifespan of approximately 25 days in control animals would not appear to put an unbearable burden on space requirements for the laboratory. The laboratory would have death checks to make instead of calculating or weighing to get T/Cs.

Data compiled from various experiments where percent ILS was obtained after early treatment with selected antimetabolites are shown in table 6. The antimetabolites tested in our laboratories have not had great activity against the Lewis lung tumor. Arabinosylcytosine produced a +37% ILS on a q3h schedule and only 12% on a qd, Days 1–15 schedule. Arabinosylcytosine and palmO-ara-C are probably among the most effective antimetabolites against the sc Lewis lung tumor.

Some alkylating agents are quite active against the Lewis lung carcinoma. Comparative

TABLE 6.—Evaluation of various antimetabolites vs sc Lewis lung tumor

NSC No.	Name	Dose	Schedule	ILS (%)
63878	Arabinosylcytosine	22.5	q3h × 8, Days 1,5,9,13	>+37
135962	PalmO-ara-C	18	qd, 1–15 days	+27
63878	Arabinosylcytosine	30	qd, 1–15 days	+12
27640	5-FUDR*	33	qd, 2–12 days	+12
755	6-MP†	43	qd, 2–12 days	+10

*NSC-27640.

†NSC-755; CAS reg. No. 6112-76-1.

TABLE 7.—Evaluation of various alkylating agents against sc implanted Lewis lung tumor

NSC No.	Name	Dose	Schedule	ILS (%)
103548	Nitrosourea	15	Days 1, 8	>+316
95441	CCNU	21	Days 1, 8	>+316
26271	Cyclophosphamide	225	Day 2 only	>+210
93184	Nitrosourea	18	Days 1, 8	+108
88104	Nitrosourea	27	Days 1, 8	+53
82196	BIC	44	qd, 1–9 days	+19

lifespan data of selected agents are shown in table 7. Cyclophosphamide, as mentioned, is very effective in early treatment against the sc Lewis lung tumor. Methyl-CCNU has consistently been effective in producing cures against the advanced Lewis lung tumor. NSC-103548 is about as effective as methyl-CCNU. Other nitrosoureas have more moderate activity against the Lewis lung tumor. 5-[3,3-Bis-(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide (BIC; NSC-82196) is not effective against this tumor.

Dr. Montgomery, Director of the Organic Chemistry Research Department, Southern Research Institute, has recently analyzed data from experiments in which 25–30 nitrosoureas were tested against the established (400-mg) sc Lewis lung tumor. Relative effectiveness was calculated using percent ILS, and nitrosoureas were ranked according to activity. Dr. Montgomery is of the opinion that the percent ILS separates the most effective nitrosoureas against this tumor, the moderately effective nitrosoureas, and those nitrosoureas that are relatively ineffective.

To summarize very briefly, we have presented data compiled largely in our laboratories regarding the biologic characteristics of the sc implanted Lewis lung tumor. Four possible methods of evaluating data after early treatment of the sc Lewis lung tumor have been discussed.

LIST OF COMPOUNDS

Arabinosylcytosine: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride; ara-C

BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan

Methyl-CCNU: NSC-95441; CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-

NSC-82196: CAS reg. No. 5034-77-5; imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]-

NSC-103548: cyclohexanecarboxylic acid, *trans*-4-[3-(2-chloroethyl)-3-nitrosoureido]-, ethyl ester

PalmO-ara-C: NSC-135962; cytosine, 1-β-D-arabinofuranosyl-, 5′-palmitate

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